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CHRONIC ORGANIC ARTERIAL DISEASE*

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BOSTON

WHEN the arterial supply to a limb is diminished, certain symptoms and disability follow. These vary more with the rapidity and degree of the diminution of blood flow than with the nature of the disease responsible for the obstruction. Since these effects are so profound, it is of consequence to focus considerable attention on the resultant syndrome of arterial insufficiency, as well as on the specific "background disease."

I shall here attempt a summary of present-day concepts of arterial insufficiency and of the commonest background diseases. I shall not discuss localized or acute disorders, such as aneurysm, embolism or trauma to arteries, nor functional disorders such as Raynaud's disease.

PATHOLOGY

Aside from syphilitic arteritis, which is uncommon in the limbs, most chronic organic disease of the peripheral arteries falls into two main groups: arteriosclerosis and thromboangiitis obliterans.

Arteriosclerosis

We may quickly dispose of a frequent but innocuous form of arteriosclerosis, namely Mönckeberg's sclerosis. In this disease the media of arteries is rendered fibrotic and calcified. The calcification is even and extensive but the disease gives rise to no arterial insufficiency, since the lumen is not encroached upon (Fig. 1). While the finding of pipe-stem vessels by x-ray is not indicative of arterial obstruction, neither does it rule it out, since the sclerosis may be complicated by the obstructing form next to be described.

"Atherosclerosis, the important form of arteriosclerosis, a metabolic disease,"[1] is characterized by the storage of cholesterol within the intima of the artery, entailing at its very inception an obstruction of the vessel (Fig. 2). While it is mainly a disease of middle age, the disease may start in early life or childhood in the presence of a high blood cholesterol, as occurs in diabetes. While atherosclerosis is widespread in the body, serious peripheral involvement is usually limited to the lower limbs. The veins are practically unaffected, and the smaller arteries and arterioles are likewise spared, except in the complicating arteriolar sclerosis of hypertension (Fig. 4). Inflammation of the artery does not occur. Calcification of the atheroma supervenes but bears no relation to the size of the atheroma. X-ray may, therefore, not show any arterial calcification or only a small amount in a spotty, irregular pattern, even when the artery is completely obstructed by the atheroma (Fig. 6).

FIGURE 1. *Mönckeberg's Sclerosis in an Anterior Tibial Artery.*

The media is transformed into a calcified tube, which has fractured on sectioning. The lumen is unobstructed. The veins and nerve trunks are normal.

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The atheroma may enlarge so as entirely to obstruct the artery, but more frequently thrombosis completes the obstruction. Organization of the thrombus follows, but contrary to the process in veins, the subsequent recanalization usually fails to produce any sizable lumen. This must be remembered in considering prognosis for the arteriosclerotic patient.

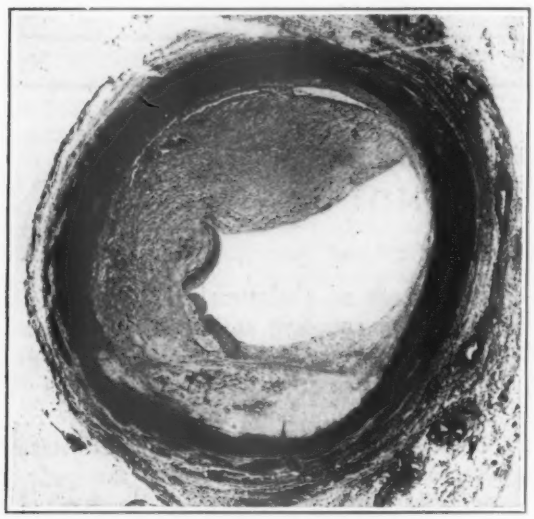

FIGURE 2. *Atherosclerosis in a Popliteal Artery.*

The lumen is considerably obstructed by an atheroma. Only minute collections of calcification are found within this structure, and bear no relation to the degree of obstruction. There is no inflammation and no involvement of the small arteries, the veins or the nerves. The media is relatively normal but has taken a dark stain.

FIGURE 3. *Thromboangiitis Obliterans in a Superficial Vein of the Leg.*

This process is identical with that present in the arteries. There is marked inflammation, with cellular infiltration throughout the entire vessel, extending to the perivascular region. Giant cells are present in the tissue filling the lumen. When found, this picture is diagnostic of the disease.

Buerger's Disease or Thromboangiitis Obliterans

This disease starts somewhat earlier than arteriosclerosis, occurring in the late twenties, thirties and forties. Moreover, it involves men almost exclusively, being extremely rare in women. Recently it has become apparent that the disease occurs in men of other races about as frequently as in those of Jewish descent. The ultimate etiology is unknown, but tobacco plays an undoubted role, since the disease is practically limited to those who have smoked heavily for many years, and spontaneous remissions occur oftenest in those who cease smoking entirely.

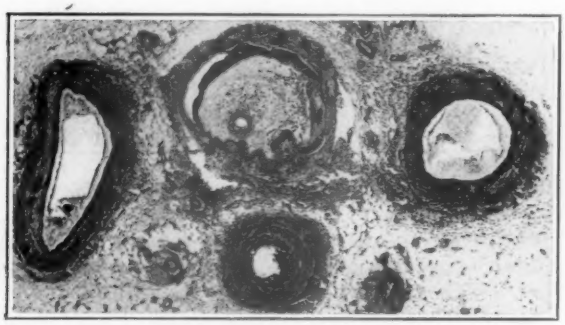

FIGURE 4. *Late Stage of Atherosclerosis in the Anterior Tibial Neurovascular Bundle.*

The artery is completely occluded by an old atheroma. There is an incomplete ring of calcification in the periphery of this material. The smaller arteries, the veins and the nerves are all free of disease.

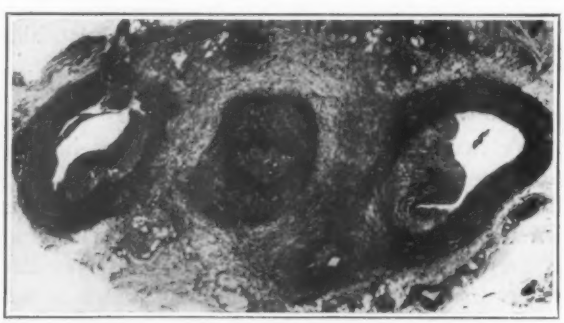

FIGURE 5. *Late Stage of Thromboangiitis Obliterans in the Anterior Tibial Neurovascular Bundle.*

The lumen of the central artery is filled by an organized thrombus. Inflammatory tissue is seen in the smaller artery below, as well as in the venae comites. Extension of the inflammation beyond the confines of the vessels encroaches on the small nerve trunks.

Inflammation is a prominent feature (Fig. 3), and thromboangiitis obliterans differs further from

arteriosclerosis in that it involves vessels of all caliber, and not only arteries, but veins as well (Fig. 5). The closure of the small arteries renders them unfit as pathways of the necessary collateral circulation, and is one factor making this disease more resistant to treatment than is arteriosclerosis.[2] The upper extremities are attacked somewhat oftener than in arteriosclerosis. Moreover, like arteriosclerosis, Buerger's disease may be widespread, involving the blood vessels of the viscera. Thus Averbruck and Silbert,[3] in an autopsied group of patients with the disorder, found that 40 per cent had died from one or more vascular accidents in the viscera, predominately the heart, brain and intestines.

FIGURE 6. *X-Ray Arteriogram of an Arteriosclerotic Femoral Artery.*

This was made following an injection during life. The artery is completely obstructed at the midthigh. Nevertheless the calcification ("calc.") *is minimal. Note the fine collaterals at the end of the femoral artery and at the knee.*

While the involvement of arteries and veins is probably simultaneous, "migrating phlebitis" of the superficial veins may be the earliest symptom. The veins attacked are frequently the dorsal venous arch of the foot, the saphenous veins or the veins of the forearm. The phlebitis typically skips from one small segment to another, lasting one to four weeks at each site. A man showing such a phlebitis should be watched for other evidence of Buerger's disease. Sometimes biopsy will establish early diagnosis.

The characteristic lesion is common to both the veins and arteries. It consists of a proliferation of the intima, containing multinucleated giant cells (Fig. 3). These cells may not always be seen. More constant is the presence of histiocytes, lymphocytes and polymorphonuclear leukocytes. The media and adventitia likewise show inflammatory exudate of both acute and chronic character, and the inflammation, indeed, extends beyond the vessel wall to encroach on the perivascular structures, notably the nerves. This neuritis would seem to account for much of the particularly excruciating pain of the disease.

Thrombosis soon accompanies the inflammation. Organization is somewhat more active than in arteriosclerosis, but recanalization is of no great importance (Fig. 5).

Secondary Changes

When an artery is the seat of organic disease, the irritation of its sensory nerves may initiate a reflex contraction of distant segments of that artery, and indeed all the arteries and arterioles of the limb. When this vasoconstriction is marked, it may additionally obstruct an already impaired circulation. This occurs infrequently in arteriosclerosis but is occasionally important in Buerger's disease. Since the reflex is mediated by the sympathetic nervous system, the vasoconstriction can be tested by measuring the surface temperature of the limb before and after anesthesia or other inhibition of the sympathetic tone. If much vasoconstriction is thus demonstrated, some improvement can be expected from surgical attack on the sympathetic nerves. The occasions when such operative treatment is necessary in these organic diseases are, however, infrequent, and this matter will therefore not be discussed further in this paper.

In arterial insufficiency from any cause, the closure of the major arteries makes it necessary for the blood to flow through the smaller communicating vessels, which we term the collaterals (Figs. 6 and 7). As these collaterals increase in size, the aggregate of their openings becomes equal to, or even exceeds, the caliber of the blocked arteries. However, this does not ensure the delivery of an equivalent amount of blood, since the flow in small vessels is not directly proportionate to their size, but rather to the square of their diameters. In these small arteries the pulse wave is damped and the blood oozes through under a lowered pressure (Fig. 9). In effect, then, while it is desirable and necessary to increase the size of the collaterals, in no case can these vessels transmit the quantity of blood passing through the previously normal arteries.

At present, at least, we have no means of restoring the major arteries involved in arteriosclerosis or Buerger's disease. It is thus obvious that the

patient can never expect a return of perfect function in the affected limb, as the new non-pulsatile circulation cannot support an active metabolism.

This thesis acquires verification when we examine a group of animals whose circulation is normally similar to this abnormal flow in the human subject. Reference is made to sloths, anteaters and lemurs. In these animals, the main artery to the limb breaks up into a great group of fine vessels at the very root of the extremity (Fig. 8). This vascular arrangement can be correlated with the sluggish muscular habits of these animals.[4]

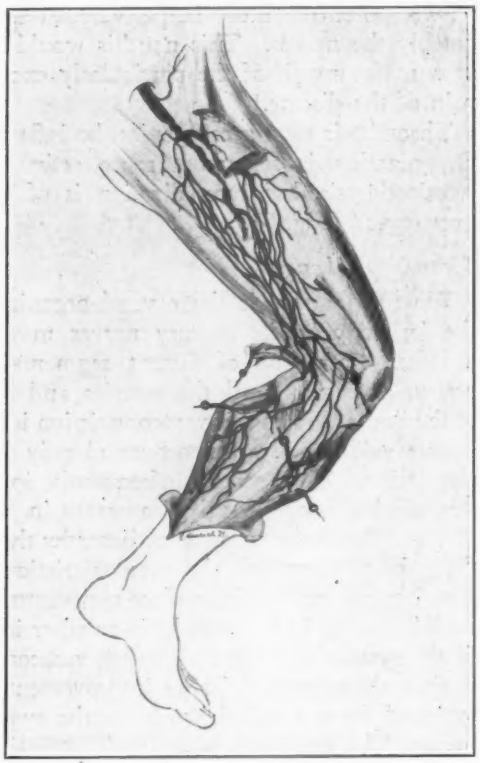

FIGURE 7. *Collateral Circulation after Organic Obstruction of the Major Arteries.*
This sketch is drawn in accordance with arteriograms. Compare with Figure 8.

FIGURE 8. *Normal Circulation of the Sloth.*
The major limb artery breaks up into a great number of fine vessels, accompanied by corresponding veins (Hyrtl[15]).

DIAGNOSIS

Clinically, before one can accurately diagnose the specific nature of the background disease he must establish the presence of arterial insufficiency. As a basis for judging the adequacy of the circulation, we may list the following characteristic functions of a normal blood supply, and then consider how these may be changed by arterial obstruction: (1) continued muscular action can be carried out with ease and full vigor; (2) the skin is maintained in a warm state; (3) an adequate nutrition of the peripheral nerves ensures normal sensation; (4) there is efficient defense against injury of various types; (5) the skin color is a characteristic pink; (6) the pulsations are adequate.

Muscle action. In high-grade obstruction, even occasional muscular action is weak. The muscles are apt to be atrophied, partly from malnutrition, partly from disuse. If the obstruction is moderate, a single muscular contraction may be powerful, but continued use is impossible. This occasions the syndrome called "intermittent claudication," a symptom of arterial insufficiency from any cause. Typically, after walking one or two blocks the patient is seized by a severe cramping pain in the calf or sole of the foot. He recovers on resting a few minutes, and again can walk the same distance as before, again to be seized by the cramp, and again recovering after his rest. Moreover, the distance traversed before the cramp and the time for recovery are usually constants for any one patient, and change only with further involvement of the arteries or with improvement of the collateral supply.

Skin temperature. Coldness of the affected limb is a usual symptom of arterial obstruction. This coldness can be felt by the examiner's hand, but

the part should be exposed for at least fifteen minutes in a cool room (about 68°F.). Because of the diminution of the warm blood stream, the fingers or toes are apt to be seriously frozen in weather that would not affect the normal person.

Sensation. Sensory changes are frequent in arterial insufficiency, since the nerve tissue is most sensitive to the loss of blood supply. Either hypesthesia or hyperesthesia may result. Complete anesthesia is rare in arterial insufficiency, and points to a primary nerve lesion.

Hypesthesia is more frequent in arteriosclerosis and is less common in cases of Buerger's disease. The distribution is glove-like, corresponding to arterial fields rather than to those of the nerve trunks.

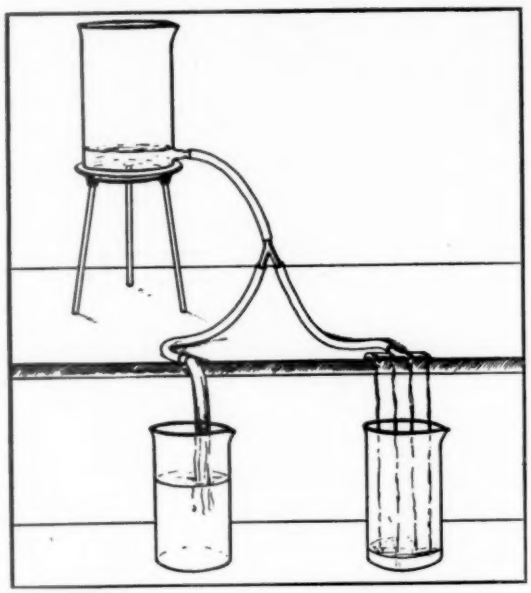

FIGURE 9.

The amount of liquid flowing through one large tube, for example a normal major artery, contrasted with that flowing through an equivalent area in several small tubes, for example the collateral arteries in Figures 6 and 7.

Hyperesthesia and pain vary somewhat with the degree of the insufficiency. Pain is apt to be more pronounced in Buerger's disease than in arteriosclerosis, and is especially severe in ulcerated areas.

Defense and repair. With blood insufficient to carry on normal activity, it is not surprising that there should be a diminished defense against injury — traumatic, thermal or bacterial. Trauma of trivial magnitude is apt to cause necrosis. Then, through the diversion of blood to the injured part, or because of the entrance of bacteria, there may follow massive gangrene or, especially in arteriosclerosis, a disseminated infection. We have all seen gangrene initiated in these patients by the cutting of an ingrown toenail, the stubbing of a toe or the application of some salicylic acid preparation (Fig. 10). I have frequently observed a long-lasting superficial ulceration where adhesive plaster has been removed from a diseased foot. Certainly this material should never be applied to such toes or feet.

FIGURE 10. *Necrotic Ulcer of the Foot in Thromboangiitis Obliterans.*

This was caused by the application of a proprietary salicylic acid corn cure.

It should be remembered that epidermophytosis is particularly likely to be a serious infection in the presence of vascular disease. In its treatment, only the mildest of antiseptics should be used. Especially contraindicated are iodine and ointments containing salicylic acid.

Skin color. Changes in the skin color depend not only on the degree of occlusion in the major arteries but also on the patency of the nonpulsatile collateral circulation. With the patient lying flat, the color of the foot may be quite normal. When the foot is elevated, to an angle varying with the severity of the insufficiency, the skin shows a waxy pallor, called "blanching on elevation." The change is due to the withdrawal of the venous blood from the foot and the inability of new arterial blood to reach it, since the abnormally low arterial pressure of the limb cannot supply a column of blood to the elevated part.

If the patient then stands, or hangs his legs over the edge of the bed or table, the pallor is succeeded by a dark red color, the "rubor of dependency." This rubor indicates the presence of a large quantity of blood in the skin vessels and is dependent on a "reactive hyperemia." Lewis[5] designates this hyperemia as the "discharge of the circulatory debt." He holds that during the elevation, the circulation being particularly inadequate, the products of metabolism are stored in the tissues. These metabolites produce a dilating effect

on all the vessels of the part. The vessels cannot fill, however, until the foot has been placed in a dependent position. It is then that hyperemia occurs. This reaction forms the basis of Buerger's exercises.

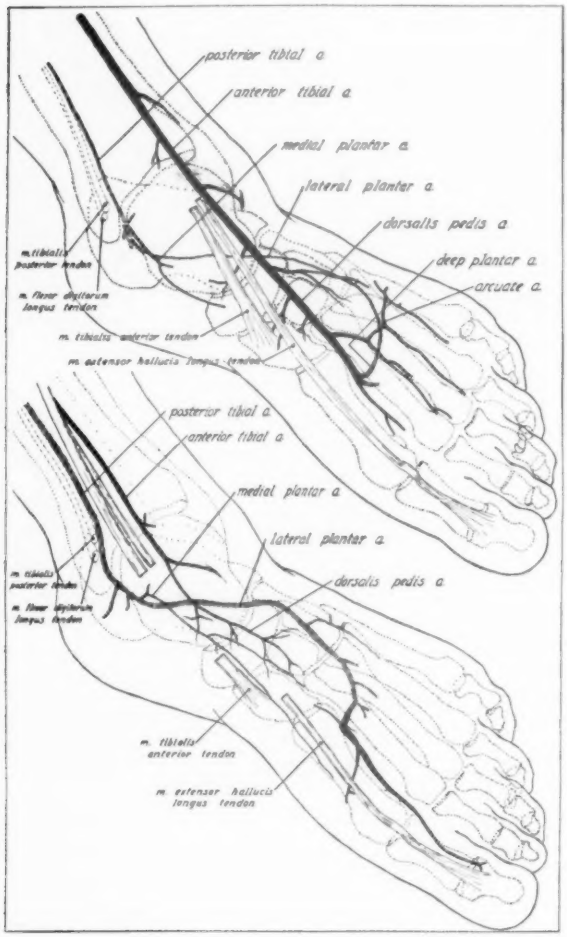

FIGURE 11. *Two Varieties of the Normal Arterial Supply to the Foot.*

Above is the more typical arrangement, with a large dorsalis pedis artery and a very small posterior tibial artery. The latter breaks up into medial and lateral plantar arteries. The dorsalis pedis ends as the deep plantar artery, which perforates the first metatarsal space to join the lateral plantar artery.

Below is an atypical arrangement found with sufficient frequency to be important. Here the posterior tibial artery is the larger vessel. Its terminal lateral plantar branch is the main distributing artery to the foot. It ends on the dorsum after perforating the first metatarsal space. The dorsalis pedis artery is insignificant, and would be "absent" clinically.

Pulsation in the arteries. In the upper extremities one must palpate the axillary, brachial, radial and ulnar arteries. In the lower extremities one must examine the external iliac, femoral, popliteal, dorsalis pedis and posterior tibial arteries. The popliteal is best palpated with the patient prone and the leg flexed by the examiner's hand. The posterior tibial can be palpated just below and behind the medial malleolus.

The importance of this latter vessel is not sufficiently appreciated. Let it be remembered that a substantial number of people are born with a small or absent dorsalis pedis artery. In such cases the posterior tibial will be large and will compensate for the absence of the former artery (Fig. 11). An absent dorsalis pedis pulsation, therefore, does not necessarily indicate disease. However, since this anomaly is usually symmetrical, the absence of a single dorsalis pedis, or a single posterior tibial pulsation, is more likely to be due to disease than to anatomical variation.

Because the pulsation of the main arteries is a crucial matter, it is wise not only to palpate the vessels but also to measure the pulsation by some objective means. An accurate measurement can be made, both of the arterial pressure and the size of the pulse expansion, by means of the Pachon oscillometer. An approximate measurement of the pulsation may likewise be obtained by the use of the simple aneroid manometer.

Symptoms of insufficiency may arise with the loss of one or both pedal pulses, and with diminution in the popliteal pulse. When symptoms are severe the femoral artery is likely to be closed in the lower third of the thigh, with the popliteal and pedal pulses absent. Less frequent, but by no means rare, is obstruction of the upper femoral or even of the external iliac artery. Variations in symptoms, especially claudication, have been shown to depend also on the degree of occlusion of the small arteries supplying the muscles.[6]

The diagnosis of arterial insufficiency will be apparent from the history and examination as it pertains to the functions we have just considered. Once this is established, one should attempt the diagnosis of the background disease. Syphilis of the arteries must always be ruled out. Arteriosclerosis is by far the commonest disease. It is the likely diagnosis when arterial obstruction is found in a middle-aged man or woman, particularly if the patient is diabetic. Buerger's disease is the more likely if the patient is a young man who uses tobacco, and the diagnosis is strengthened if there is a history of migrating phlebitis.

TREATMENT

Chronic Insufficiency

Specific treatment of the background disease. Our meager knowledge of the etiology of arterial disease gives us a poor basis for the specific treat-

ment of these diseases. I am aware of no treatment that will remove the obstruction from the already blocked arteries. It is not even sure that our efforts will avail in arresting the progress of the disease to other arterial segments yet unobstructed.

In arteriosclerosis, we advocate the avoidance of an unduly disturbing life; the elimination of toxins, bacterial or chemical, including tobacco; and moderation in the intake of cholesterol-rich foods, especially eggs and dairy and pork products.[7] In line with the lowering of excessive blood cholesterol, hypothyroidism and diabetes should be adequately controlled. Thyroid should never be used in large doses and not at all in the face of acute insufficiency, since the resultant rise in metabolism in the diseased part will put a further demand on an already inadequate circulation. In diabetes the diet should not contain undue amounts of the foods just mentioned.

Because of the apparently specific effect of tobacco on thromboangiitis, smoking is absolutely contraindicated in that disease.

Treatment of the arterial insufficiency. The patient with chronic insufficiency must be advised not to overtax his circulation by excessive standing or walking. Moreover, he should avoid the risk of trauma, and should not get his feet cold or wet. Corns should be treated only by careful superficial trimming, and by the wearing of well-fitting shoes. Ingrown toenails should be treated conservatively. No strong chemicals should be used on the feet. The patient should wash his feet daily in warm soapy water, dry them gently and rub in a little vaseline or lanolin to keep the skin supple. Soft woolen socks cushion the feet well, and should be worn the year around. The shoes must be large and of soft leather, and if hypesthesia is present the patient must keep the diminished sensation in mind when being fitted.

It has been pointed out that tobacco may play a part in the etiology of both important background diseases. We must mention additionally that tobacco must not be used in the presence of arterial insufficiency from any cause, because of its profound vasoconstrictive effect. Lampson,[8] measuring this effect, found that smoking a single cigarette reduces the blood flow to the arm from 40 to 80 per cent. It will be readily appreciated that such a diminution may be quite deleterious in the face of an already existing insufficiency.

In my experience the application of alternating suction and pressure has been the most effective of the methods to increase the collateral flow in the majority of patients. This treatment is based on the sound principle that a small negative pressure applied distally will increase the velocity and quantity of the blood flow during treatment, and, by repetition, will produce a lasting dilatation of the collateral vessels. Elsewhere I[9] have described the use of a gentle heating of the limb during the treatment in order to relieve any incidental vasospasm.

Before treatment is started, one must make sure that there is neither a complicating venous thrombosis nor any pyogenic infection in the limb, since the treatment may precipitate the loosening of an embolus or the dissemination of bacteria. Moreover, the physician should personally attend to the details of the treatment, varying them for the individual patient.

When a suction-pressure apparatus is unavailable, or when it is contraindicated, Buerger's exercises constitute the mainstay of treatment. The exercises consist essentially of a periodic elevation of the limb followed by dependency. The mechanism of its effect in dilating the collaterals has been discussed in the section on symptomatology. The exercises should be done in a warm room, with the patient lying on a bed, and with the lower limbs undressed. The elevation is carried out by resting the legs against some padded object, like a back rest, an inverted chair or a hinged Buerger's board. Elevation is continued only until blanching is maximal. This takes an average of two minutes. The patient then sits with the legs hanging freely over the edge of the bed for another two minutes. During this second position the patient may perform active exercises of the feet in order to strengthen the muscles and diminish stiffness. If the patient is feeble, a third period of simple horizontal rest follows for one minute. This cycle, as enumerated, occupies five minutes, and should be repeated for the total of one hour at a sitting. To produce a substantial effect, the patient must exercise at three or four sittings a day, totaling three or four hours.

The intravenous injection of hypertonic saline is extensively used in some clinics, and undoubtedly increases the collateral flow, especially in Buerger's disease, but I believe it less efficient than either suction-pressure treatment or Buerger's exercises.

Diathermy and radiant heat are measures mentioned only to be discouraged. Local heat is known to increase greatly the arterial flow in a limb when the vessels show no organic obstruction. But this increase, according to Freeman,[10] is brought about by an increase in the local metabolism and a corresponding concentration of the vasodilatory metabolites. Given a condition where the arteries are organically blocked, the necessary increase in blood flow cannot occur, and the stores

of the already undernourished tissues are further depleted. This cannot fail to be of harm to the extremity.[11] It should further be remembered that intense heating, such as is supplied by the diathermy apparatus, will actually coagulate the tissues unless there is an actively circulating blood stream to carry the heat away as it is produced. This can be easily demonstrated by the cooking of a piece of beef by diathermy. Similar changes may be expected if heat is applied to a limb whose circulation is impaired. Injury by heat is suggested in patients subjected to such treatment by an immediate increase in pain or the advent of gangrene.

General management. Arterial disease, with its disability, pain and the fear of amputation, demands considerable attention on the physician's part to supervise the general health and morale of his patient. We may point out a few details of particular importance. Vitamin-rich food and vitamin concentrates should be given, since general debility or loss of appetite may result in a depletion of vitamin reserves. Diminution of the circulatory functions by reason of anemia or cardiac weakness should be appropriately treated. Of importance also are fresh air, sunshine and the avoidance of unpleasant emotional experiences.

Acute Insufficiency or Pre-Gangrene

In the face of acute insufficiency, with necrosis present or threatening, the patient must be put to bed in a hospital.

Because elevation sharply diminishes the blood supply to such a limb, it is obvious that it should be kept relatively horizontal. A small pad should be placed under the Achilles tendon to avoid pressure or abrasion of the heel. It is advisable to keep the bedclothes off the feet, but bearing in mind the effect of heat, the cradle should not be heated.

Both the specific and general measures used in treating chronic insufficiency should be applied in the acute state. Pain may be an outstanding symptom here. Suction-pressure treatment will often diminish it markedly, but some sedative may have to be used. Alcohol is particularly useful, since it is a fair peripheral vasodilator, as well as a sedative and analgesic. Moreover, Leary[12] has indicated that, contrary to former belief, the frequent use of alcohol may tend to prevent arteriosclerosis.

Ulceration and Gangrene

As a rule, any patient showing ulceration should be in bed and in a hospital. Ulceration brings with it the possibility of infection. It is especially in these patients, therefore, that diabetes if present must be immediately and adequately controlled.[13] The diabetic arteriosclerotic patient stands in contrast to the patient with thromboangiitis obliterans, in whom a spreading infection is rare.

When the ulcer presents no obvious infection and also gives no great pain, it should simply be kept covered with a sterile dressing. Gauze wet with hexylresorcinol solution is excellent for this purpose. If the wound is mildly infected, it may be treated by frequent changes of warm boric acid compresses. Buerger's exercises should be carried out, although active exercise is contraindicated. As soon as the clinical and laboratory evidence of infection is gone, suction-pressure treatment should be used, both to heal the ulceration and to give a better circulation for future use.

It is well to keep in mind that ulceration of these toes or feet frequently leads down into the tendon sheaths or the bones. In the first instance infection of the sheaths will result and must be treated by surgical drainage. If the circulation is deemed to be too precarious to support healing of such a deep process, early amputation should be considered. If the ulcer overrides a sinus leading into bone, or if an x-ray study demonstrates bony destruction, healing will be difficult. Ordinarily amputation at some level is necessary, although I have seen spontaneous separation of a sequestrum and healing after intensive suction-pressure treatment.

If there is reason to suspect a rapidly spreading infection, especially common in arteriosclerosis (both diabetic and non-diabetic), conservative measures must not be relied on too long. Under these conditions amputation is frequently an emergency measure. If the patient is very ill, a true guillotine amputation should be performed, and reamputation done some few days later.

In some patients, pain is so excruciating as to prevent the proper carrying out of conservative measures. If it is determined that this one factor is preventing a favorable outcome, desensitization of the affected part should be accomplished by a temporary interruption of the sensory nerves by crushing or alcohol injections.[14] This procedure should not be done if the condition of the limb is deemed altogether hopeless, apart from any consideration of pain.

Finally, a massive necrosis or gangrene demands amputation. This should not be delayed, since infection may supervene at any time. The level of amputation must be decided according to the individual problem, and we have come to realize that amputation need not always be performed at the midthigh. Moreover, it should be mentioned that some believe that in Buerger's disease spontaneous separation of the gangrenous part should

be allowed. I do not subscribe to the constant application of this rule.

SUMMARY

Most chronic organic occlusion of the peripheral arteries is caused either by arteriosclerosis or by thromboangiitis obliterans. The former is a metabolic disorder occurring in men and women of middle age. In diabetes the disease may occur in relatively young patients. Thromboangiitis obliterans, or Buerger's disease, occurs, almost without exception, in young men in the latter part of the second or in the third or fourth decade. The patients are usually heavy tobacco smokers. The disorder is inflammatory and involves both veins and arteries. Involvement of the superficial veins in a "migrating phlebitis" may call early attention to the disease.

Obstruction of the major arteries by any disease diverts the arterial flow through smaller collateral channels. This results in a diminished blood-flow or arterial insufficiency, with symptoms which are independent of the "background disease" producing the obstruction.

The symptoms and signs of arterial insufficiency may be conveniently considered under the following headings: (1) muscle action is weak, and intermittent claudication may develop; (2) the limb is abnormally cold; (3) hypesthesia, hyperesthesia and spontaneous pain may result from an ischemic neuritis; (4) there is diminished resistance to injury, and ulceration may result from trivial trauma; (5) the toes and feet show blanching on elevation, and rubor on dependency; (6) the pulsation in the affected arteries is small or absent.

The specific treatment of arteriosclerosis consists of the avoidance of mental and physical stress, the cessation or diminution of tobacco smoking, and moderation in the intake of cholesterol-rich foods. In Buerger's disease it is essential that the patient use no tobacco whatsoever.

The treatment of the arterial insufficiency may be divided into the general care of the feet, the avoidance of tobacco, and the increase of the collateral blood-flow. In the writer's experience this latter is best accomplished by the use of alternating suction and pressure. Such treatment is contraindicated in the presence of infection or thrombosis. Under these conditions, or when the apparatus is not available, Buerger's exercises should be used.

Attention should be paid to the general management of these patients. Optimum general health should be maintained, and the patient encouraged in his fight against pain and disability.

In the acute states of pre-gangrene, ulceration or gangrene, the patient should be in bed in a hospital. The procedures previously described are used with the addition of certain measures to diminish pain and to prevent infection.

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Discussion

Dr. Laurence B. Ellis, Boston: Dr. Edwards in his excellent summary of this subject was wise to emphasize the problem as one of arterial insufficiency. In considering the diagnosis and treatment of clinical disorders one should always try to understand the nature of the disturbed physiologic process which is occurring, and it is particularly desirable to emphasize this in conditions such as those here under discussion, where knowledge of the etiology is so unsatisfactory.

It is fair to consider the problem of organic arterial disease, from the physiological angle, as one of supply and demand, in which the supply of blood to certain tissues is impaired through insufficiency of the channels carrying the blood, that is the arteries. From the therapeutic standpoint the problem can often be solved for a time by cutting down the metabolic demands of the tissues by rest, maintenance of a suitable external temperature and avoidance of local infection.

The attack from the viewpoint of increasing the supply of blood is more complicated, and necessitates a knowledge of the physiological factors which alter the caliber of the arteries. Normally the arteries are under a certain tone, of which part is intrinsic in the muscle fibers themselves and part is controlled by the vasomotor nerves. This tone is affected in a number of ways, which may be roughly classified as emotional and other reflex stimuli; chemical stimuli, such as circulating hormones, for example epinephrine, circulating products of tissue metabolism, for example histamine and carbon dioxide, and extrinsic factors, for example alcohol and tobacco; and physical stimuli, such as heat and cold. In health the reserve capacity of the arterial bed is such that the supply of blood to the tissues is adequate even under conditions of markedly increased local vascular tone. In states of

arterial disease, however, this reserve may be so impaired that in managing such disturbances it is important to take advantage of physiologic conditions which dilate vessels and to avoid those which produce constriction. This is particularly true because there is often a tendency for arterial spasm to occur superimposed on the organic arterial disease.

There is therefore good physiological basis for the advice we give such patients in the management of their lives. We tell them to rest, to avoid subjecting the diseased extremities to extremes of heat and cold and to avoid local trauma and infection, all of which cut down the metabolic demands of the tissues. We tell them to avoid states of emotional tension and fatigue, which may result in reflex vasoconstriction, as well as in the liberation of hormones which may heighten vascular tone. They are advised to avoid tobacco because it may be a vasoconstrictor and are allowed small amounts of alcohol because it is a vasodilator. Dr. Edwards has already explained the physiological basis for Buerger's exercises.

There are a number of well-known clinical tests for evaluating the ability of blood vessels of an extremity to dilate and increase the blood flow to the affected region. Recently, in Dr. Weiss's laboratory at the Boston City Hospital, Drs. Stead and Kunkel have carried out some interesting experiments with a foot plethysmograph, constructed on the principle of Hewlett and Van Zwaluwenberg. With this apparatus a fairly accurate quantitative expression of local blood flow is obtainable, and it may well be that such a device will eventually have a place in measuring peripheral blood flow, not only in the experimental laboratory but also in clinical practice.

NERVE INJURIES IN SUPRACONDYLAR FRACTURES OF THE HUMERUS IN CHILDREN

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BOSTON

SUPRACONDYLAR fracture of the humerus is the elbow fracture most frequently encountered in children. Much has been written on the circulatory complications of this injury, but there is little in the literature in regard to the complication of nerve paralysis. The radial, median and ulnar nerves run in close proximity to the lower end of the humerus, and they may be injured either at the time of the fracture or later during attempts at reduction.

A review of the literature on supracondylar fractures which has appeared in the last decade reveals several references to associated nerve injuries. In a series of 330 supracondylar fractures treated at Bellevue Hospital, New York City, and reported by Siris,[1] there were 11 cases with nerve paralysis, an incidence of 3 per cent. Seven of these paralyses were radial and 4 were ulnar. All patients eventually recovered power. Sorrel and Sorrel-Dejerine[2] recently reviewed 207 supracondylar fractures and found 16 cases with nerve involvement, an incidence of 7 per cent. There were 7 ulnar, 4 radial, 4 median and 1 combined median and ulnar paralyses. These writers recommend exploration of the nerve if beginning recovery does not occur within fifteen days. In a series[3] of 83 supracondylar fractures treated at the Massachusetts General Hospital there were 2 with nerve palsies, an incidence of 2 per cent. One of these was radial and the other was a combination of median and ulnar. Both lesions cleared up spontaneously. Platt[4] observed in seven years only 4 cases of radial palsy associated with this fracture, and asserts that they are rare. In 3 of these cases complete recovery occurred. Platt has also seen 1 case of median and 3 of ulnar nerve paralysis, in all of which the patients recovered. Jones[5] observed that the median nerve was occasionally injured in supracondylar fractures, either as an immediate complication of the fracture or as a result of attempts at reduction. He believed that direct injury to the radial nerve was rare. Dunn[6] asserts that in his experience the median is the nerve most commonly injured, but that in some cases a paralysis of the ulnar or radial nerve has appeared. Recovery took place in all his cases.

During the three-year period from January 1, 1936, to January 1, 1939, 71 cases of supracondylar fracture of the humerus in children were treated on the Bone and Joint Service of the Boston City Hospital. Six of these cases, or approximately 8 per cent, were complicated by nerve involvement. In 4 cases the radial nerve alone was affected, in 1 the median nerve alone, and in 1 all three nerves, the radial, median and ulnar. It was thought worth while to inquire into the probable cause of the nerve injury in each case, and to determine the time of return of function and the final degree of nerve recovery.

CASE REPORTS

CASE 1. R. C., a 7-year-old boy, was admitted to the Out-Patient Department on January 9, 1936, 12 hours after having fallen from a chair and injured his right elbow. On admission it was found that adhesive tape had been applied to the elbow in a circular fashion so tightly that the circulation was impaired and the patient had a complete median nerve paralysis in the hand. There was

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inability to oppose the thumb or flex the index and middle fingers, with loss of sensation over the median distribution in the hand. X-ray examination revealed a supracondylar fracture (Fig. 1). Reduction was attempted

FIGURE 1. *Case 1. X-Ray Photograph on Admission.*

under gas anesthesia, but the position obtained was unsatisfactory (Fig. 2) and the patient was sent into the hospital. Because of the marked swelling, the second reduction was delayed and the elbow was placed in a sling at a right angle. One week after injury, when the swelling had subsided, a satisfactory reduction was obtained under the fluoroscope (Fig. 3). Four days later there was

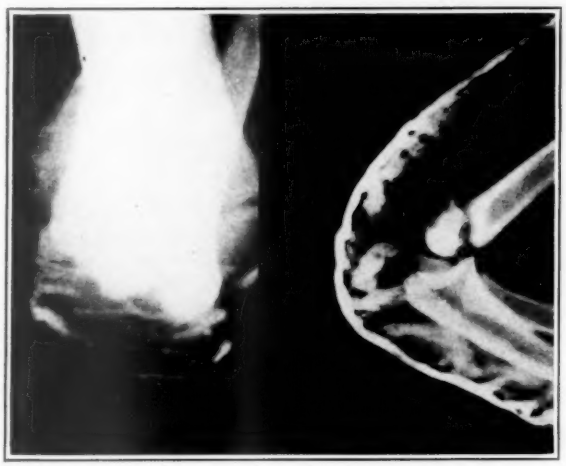

FIGURE 2. *Case 1. X-Ray Photograph after First Reduction.*

The position of the fragments is unsatisfactory.

some return of power in the fingers. The patient received physiotherapy to the hand from January 25 to February 25. There was gradual improvement in function. On March 17, 2½ months after the onset of the paralysis, there was normal power in the hand, and no area of skin anesthesia. The patient was last seen 3 months after the fracture, when elbow motion consisted of full flexion, with extension to only 100°. He could not be traced after this visit.

CASE 2. F. S., a 10-year-old boy, was admitted to the hospital April 25, 1936, 2 hours after a fall on his left arm. Examination showed a moderate swelling about the elbow with slight cyanosis of the hand. The radial pulse was strong. There was a complete radial nerve palsy, with inability to extend the wrist, abduct the thumb or extend the fingers at the metacarpophalangeal joints. X-ray films showed a supracondylar fracture of the incomplete T type. A manipulation under ether anesthesia was carried out shortly after admission, but x-ray films showed that the position obtained was poor. Two days later reduction was done under the fluoroscope and a satisfactory position was obtained. A cock-up plaster was added to the wrist. The plaster was removed in 3 weeks and a cock-up wrist cast was used to maintain the position. Motion was started at the elbow. Five weeks after onset the paralysis was still complete. Seven weeks after onset there was a good return of function in wrist and finger extension but still some weakness. Nine weeks after onset there was complete recovery of power. A

FIGURE 3. *Case 1. X-Ray Photograph after Second Reduction.*

The fragments are in satisfactory position.

check-up on May 27, 1939, 3 years later, showed normal muscle power. There was full extension of the elbow, about 5° limitation of full flexion and a 10° loss of the normal carrying angle.

CASE 3 (courtesy of Dr. Joseph H. Shortell). A. C., a 6-year-old girl, was admitted August 19, 1937. She had fallen on her left arm the day before. X-ray examination in the Out-Patient Department revealed a supracondylar fracture of the elbow. An attempt at reduction was made, but failed, and the patient was sent into the hospital. Examination showed marked swelling and ecchymosis about the elbow. A manipulation under ether anesthesia was carried out, and the elbow was placed in a plaster slab in flexion. An x-ray film showed an unsatisfactory position. Four days later a third reduction was done, under ether anesthesia, but it also was considered unsatisfactory. Following the last reduction the patient developed a complete radial nerve paralysis, as evidenced by the inability to extend the wrist, abduct the thumb or extend the fingers at the metacarpophalangeal joints. Because of the development of this complication it was felt unwise to attempt further reduction, and a cock-up splint was applied to the wrist. The child was discharged 3 weeks after admission. Six weeks after onset there was still no power in extension at the wrist. Seven weeks after onset the wrist could be extended but the thumb could not be

abducted. Three months after onset there was complete return of function in the wrist and fingers. When the patient was last seen, 9 months after injury, there was slight limitation of full extension and full flexion in the elbow.

CASE 4. L. C., a 7-year-old girl, was admitted to the hospital October 13, 1937, shortly after having fallen off a playground slide and injured her left elbow. There was very marked swelling around the elbow, and the radial pulse was decreased in volume. There was no nerve injury. X-ray examination showed a supracondylar fracture of the humerus. An attempt was made to reduce the fracture under ether anesthesia, but after 20 minutes of effort it was impossible to secure a satisfactory position. The arm was elevated on a posterior plaster shell with the elbow in 145° of extension, and icecaps were applied to control the swelling. Twelve days later, after most of the swelling had subsided, the fracture was reduced under ether anesthesia, and the elbow was placed in flexion of 15° beyond a right angle. The following day it was noted that there was a good deal of weakness in all motions of the fingers. There was no pain, and the radial pulse was strong. Four days later, because of the persistence of the finger weakness, the plaster was removed, and it was found that a complete radial palsy was present. There was also some interference with the median and ulnar nerves, as evidenced by considerable weakness in spreading the fingers and opposing the thumb. An x-ray film showed a satisfactory position of the fragments. An extension splint was applied to the wrist, and 2 weeks later physiotherapy was started for the hand and wrist. Five weeks after onset there was good motion in the fingers and the wrist could be weakly extended. Six weeks after onset there was good power in the wrist, although it was not normal. Three and a half months after onset the muscle power in the wrist and fingers was normal. Seven months after injury the range of motion in the elbow was from 90 to 135°. An x-ray film showed a small calcified hematoma on the anterior aspect of the humerus. The patient could not be traced after this visit.

CASE 5. P. B., an 11-year-old boy, was admitted to the hospital on October 21, 1938, shortly after injuring his left elbow by a fall from a fence. There was deformity and moderate swelling about the elbow. The radial pulse was good, and there were no nerve changes. X-ray examination showed a supracondylar fracture of the elbow. Two hours after admission the fracture was reduced under ether anesthesia, and the elbow was immobilized in acute flexion by means of a posterior plaster splint. X-ray films showed good position of the fragments, and the patient was discharged to the Out-Patient Department 4 days later. The first check-up examination in the Out-Patient Department, 2 weeks after reduction, revealed a complete radial palsy in the wrist and hand. The circulation was excellent, and x-ray films confirmed the good reduction. A cock-up wrist splint was added to the plaster. The elbow was mobilized 3 weeks after the fracture, with retention of the cock-up wrist splint. Physiotherapy was then started on the wrist and hand. Eight weeks after onset a slight return of function was noted. Physiotherapy was continued, and 11 weeks after the onset there was complete return of power in the wrist and fingers. A check-up examination 8 months after the fracture revealed that the elbow had 5° loss of full flexion, 15° loss of full extension and about 5° of cubitus varus deformity. Pronation and supination were normal.

CASE 6. P. L., an 11-year-old boy, was admitted to the hospital on November 2, 1938, shortly after a fall on his left arm. Examination revealed a supracondylar fracture of the left elbow, with moderate swelling (Fig. 4). The circulation and nerve supply of the hand were normal. The fracture was reduced the same day under ether anesthesia, and a plaster slab was applied with the elbow in acute flexion. Two days later it was observed that there was a complete radial palsy in the wrist and hand. The

FIGURE 4. *Case 6. X-Ray Photograph on Admission.*

position of the fragments was determined to be unsatisfactory. Another reduction was done, but the fragments could not be maintained in position. Consequently traction was applied for 10 days with the elbow at a right angle. A fair anatomical result was obtained (Fig. 5).

FIGURE 5. *Case 6. X-Ray Photograph after Reduction. Reduction was accomplished after ten days of continuous traction.*

A cast was then applied, with a cock-up wrist support. On removal of the cast 5 weeks after onset there was slight power in dorsiflexion of the wrist. Physiotherapy was instituted and continued until 11 weeks after onset, when there was full recovery of the paralyzed muscles. Seven months after fracture the elbow showed 10° limitation of extension, 10° limitation of flexion and normal supination and pronation.

DISCUSSION

In 2 cases of this series the paralysis was present prior to any attempt at reduction. One of these,

a radial palsy, we must ascribe to nerve injury at the moment of occurrence of the fracture, since the paralysis was noted on admission two hours after the accident, there being only moderate swelling about the elbow. The other, a median nerve palsy, could be laid to constriction of the elbow by adhesive tape, but it may have been caused by the fracture. In the 4 remaining cases, consisting of 3 with radial palsies and 1 with injury to all three nerves, the paralyses appeared after attempts at reduction of the fracture. Two of these showed radial palsy after one manipulation. One showed radial palsy after three attempts at reduction. One showed involvement of all three nerves after two manipulations. We must therefore ascribe the paralyses in these 4 cases to trauma to the nerves during attempts to reduce the fracture.

In every case, return of some function in the paralyzed muscle was noted before the end of eight weeks, and complete function was restored before the end of fourteen weeks. Hence it is obvious that the nerves were not severed, but simply compressed or contused.

CONCLUSIONS

Nerve injury with resulting paralysis may occur in supracondylar fractures of the humerus in children, either as a result of the fracture or from trauma during reduction. In previously reported cases the radial and ulnar nerves have been equally affected, while the median nerve has been injured only half as often as either the radial or the ulnar. In this series, radial nerve lesions predominated. The nerve is usually not severed, but simply contused. In such cases, beginning return of function may be expected within eight weeks, and a complete return of function within fourteen weeks. If some recovery does not take place within twelve weeks, the nerve should be explored. To avoid injury to nerves, all fracture reductions should be done as gently as possible. If paralysis is noted, the weakened muscles must be supported, and physiotherapy instituted.

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THE TREATMENT OF LOBAR PNEUMONIA WITH SULFAPYRIDINE*

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IN JUNE, 1938, Whitby[1] published experiments showing that a new drug, sulfapyridine, was effective in treating pneumococcal infections in mice. Since then many authors,[2-9] mainly in England, have reported the successful use of this drug in pneumonia. Evans and Gaisford[10] first used it in 100 cases of pneumonia, with only an 8 per cent mortality. Several cases of pneumococcal meningitis successfully treated with the drug are on record.[11-13] More recently Flippin et al.[14] have reported a 4 per cent mortality in a series of 100 typed pneumonias treated with sulfapyridine. Mild toxic symptoms have been frequently noted, but only rarely have they been serious. Nausea and vomiting were found by most writers to occur in about one third of the cases. Three cases of agranulocytosis,[4, 15, 16] one of acute hemolytic anemia[14] and several of drug eruption[17] have so far been recorded.

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CLASSIFICATION

The present study deals with 84 patients with lobar pneumonia treated at the Rhode Island Hospital during the winter, 1938–1939. All cases in which the diagnosis was definitely established and there were data adequate to permit evaluation of treatment were included. The criteria for diagnosis consisted of symptoms and physical signs of lobar pneumonia and, in every case, confirmation by x-ray. Pneumococci were typed in 74 cases, and were demonstrated by culture in 4 of the remaining 10 patients. Cases of hemolytic streptococcus and Friedländer's bacillus pneumonia were not included. Blood cultures were taken on all patients on admission. Blood counts and determinations of free sulfapyridine in the blood of all drug-treated patients were obtained at

frequent intervals. Oxygen was administered when needed.

Of the 84 patients 22 were treated with serum only. Ten of these were consecutive admissions in November and December, 1938, before a supply of sulfapyridine had been obtained; the remaining 12 cases were selected for this treatment in alternation with others treated by other measures. Of the 2 deaths in this group, noted below, 1 occurred in the 10 cases treated prior to January 1, and 1 in the 12 cases treated subsequently. Forty-four patients were treated with drug alone, 13 with serum and drug, and 5, entering the hospital after the fifth day of their disease, received no drug or serum therapy. During the first part of this study a strict rotation of cases in order of their admission was used in assigning them to any one group. Specifically, patients given both drug and serum were not chosen because of any greater severity of their illness. More recently all patients have been given sulfapyridine. Severe cases were present in all groups in about equal proportions. Analysis of the duration of the disease at the time of admission showed that those in the serum-treated group averaged 2.4 days, while those treated with drug alone averaged 3.2 days. In the group of patients treated with serum and drug the average duration was 2.0 days. The average age of the drug-treated patients was slightly less than that of those who were serum-treated, forty-two as compared to forty-three, while those receiving both serum and drug averaged fifty years. Extremes of age varying from fifteen to seventy-seven were present in both the drug and serum-treated groups.

DOSAGE

One hundred thousand units of serum was the usual initial dose, and more was given if needed. Sulfapyridine* was given according to the following plan: 2 gm. as an initial dose, repeated after four hours; thereafter 1 gm. every four hours day and night for twenty-four to forty-eight hours, and then 1 gm. every six hours until the temperature had remained normal for twenty-four hours. Usually between 20 and 25 gm. was found to be sufficient, and in only 3 cases was a total of 30 gm. exceeded.

RESULTS

Table 1 shows the mortality in the various groups, with the surprisingly low mortality of 2 per cent in the drug-treated group. Not included in the table are the 5 untreated patients admitted after the fifth day of their illness. Three of these died. Comparable to this group there are 10 cases, also admitted after the fifth day of their disease, included in other groups. Seven of these were treated with drug alone, and 3 with serum alone. None died.

*Supplied through the courtesy of Merck and Company, Rahway, New Jersey.

TABLE 1. *Mortality in Treated Cases.*

TREATMENT	NO. OF CASES	NO. OF DEATHS	POSITIVE BLOOD CULTURES	PATIENTS OVER 60	MORTALITY
					%
Drug alone	44	1	5	9	2 } 7
Drug and serum	13	3	1	4	23 }
Serum alone	22	2	3	3	9
Totals	79	6	9	16	
General average					8

The response to the drug shown in the temperature charts (Table 2) was only slightly less striking than that in the serum-treated group. No correlation could be found between the rapidity of drop in temperature and the day of the disease when sulfapyridine treatment was started. This is in marked contrast to the generally accepted views on serum therapy, and if borne out by other reports may indicate a particular field of usefulness for the drug in cases seen after the third day. In this series 7 cases were treated with the drug after the fifth day of the disease. Recovery was in each case much more rapid than that of 3 comparable cases treated with serum only.

TABLE 2. *Effect of Treatment on Fever.*

TREATMENT	TEMPERATURE FALL TO NORMAL					
	WITHIN 24 HR.		WITHIN 48 HR.		AFTER 48 HR.	
	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent
Drug alone	24	55	14	32	4	9
Serum alone	14	63	4	18	2	9
Serum and drug	9	69	0		2	16

It has been previously noted[14] that the blood levels of the drug do not parallel with any regularity either the dosage or the clinical improvement. Our findings are in agreement with this observation. Taking the highest figure for free sulfapyridine in the blood obtained in each patient, the average in our series was 4.3 mg. per 100 cc. Good results, however, were obtained with a concentration as low as 1.0 mg., and little effect was occasionally noted with blood levels as high as 8.0 mg.

Mild toxic reactions were present in a large percentage of the 57 patients receiving the drug. The most prominent were nausea and vomiting, which were present in well over half. In 8 cases

the drug had to be discontinued because of these symptoms, but in only 2 was this done before an adequate amount had been given. Cyanosis was present less often, and cleared rapidly on withdrawal of the drug. Severe headache was relatively rare. The significance of the transient finding of red blood cells in the urine following administration of sulfapyridine, noted in 4 cases, seems doubtful in view of the coincidental infection.

The foregoing toxic symptoms bore no apparent relation to either the blood level or to the total dose of the drug. When present, however, the nausea and vomiting could sometimes be partly relieved by cutting the dose in half, by omitting one or two doses or by changing the method of administration. Usually the drug was given crushed in warm milk, but sometimes other vehicles or none at all proved more agreeable.

TABLE 3. *Toxic Reactions Seen in 56 Cases Treated with Sulfapyridine.*

TOXIC REACTIONS	NO. OF CASES
Nausea	36
Vomiting	32
Cyanosis	22
Drug fever	8
Headache	7
Red blood cells in urine	4
Rash	2

Drug fever was noted in 8 cases. This consisted of a gradual rise in temperature, usually to not more than 101°F., and unassociated with any subjective symptoms. It occurred six to eight days after the first dose of the drug, and usually subsided after four or five days. The only case not running this benign course occurred following an excessive total dose (46 gm.), and was marked by prolonged high fever, prostration and a morbilliform rash. It is interesting that the only 2 patients in the series to receive over 40 gm. of the drug developed drug fever and drug rash. No cases of agranulocytosis or hemolytic anemia were observed. The tendency to develop slight anemia did not seem to be greater than that in any other acute infection treated by other means.

There is some disagreement in the literature as to which types of pneumococci are most susceptible to sulfapyridine.[1, 18] In our experience the drug was equally effective against all types, with the possible exception of Type 3. It may be, as has been suggested,[18] that the susceptibility varies with the strain and not the type. Of the 74 cases that were typed, 14 were Type 3. Six of these were treated with drug alone, 4 with serum alone and 4 with serum and drug. One death occurred in each group. In the series there were 9 patients with positive blood cultures. Five of these received drug alone, 3 serum alone and 1 a combination of both. Again 1 death occurred in each group. There were 16 patients over sixty years of age in the series. Nine of these were treated with drug alone, with only 1 death. Three were treated with serum alone with 1 death, and 4 were treated with drug and serum with no deaths. These three groups of patients — those with Type 3 infections, those with positive blood cultures, and those over sixty — are usually considered to carry a poor prognosis. In all of them drug treatment alone, in our small series, has proved as effective as other forms of therapy.

TABLE 4. *Types of Pneumococci Found.*

TREATMENT	TYPE OF PNEUMOCOCCUS										
	1	2	3	4	5	6	7	8	14	15	19	24
Drug alone	12		6	1	5	1	2	4	1		2	1
Serum alone	11	1	4	1	4			1				
Serum and drug	5	1	4		1			1		1		
Totals	28	2	14	2	10	1	2	6	1	1	2	1

Among the complications noted, small sterile effusions and delayed resolution were the commonest. Empyema yielding viable organisms on culture was present in only 1 case. In all, complications were present in 5 or 11 per cent of the drug-treated group, and in 4 or 14 per cent of the serum-treated group. Four or 31 per cent of the patients given both serum and drug showed complications.

DISCUSSION

Obviously the present series is too small to permit any sound conclusions as to the relative merit of sulfapyridine and specific serum in the treatment of lobar pneumonia. However, certain impressions which seem justified have been gained. Sulfapyridine has been shown to exert a markedly favorable influence on the course of the disease in the great majority of cases. The mortality figures alone are ample evidence of this. In addition the clinical course of the patients, as shown for instance in the temperature response, was favorable, and roughly paralleled that of the serum-treated cases. An attempt was made to grade all cases as to the therapeutic response, taking into consideration the number of lobes involved, the day of the disease when treated, blood cultures, age of the patient, type of infecting organism, temperature response and presence of complications. According to this classification 90 per cent of the drug-treated cases yielded good results, as compared to 73 per cent of the serum-treated group.

In 2 cases there was an opportunity to study the comparative effects of the drug and serum in the

same individual at different times. The first of these patients, a thirty-eight-year-old man, was admitted on February 6, 1939, with a Type 1 right lower lobe pneumonia. He made a dramatic recovery after receiving 100,000 units of horse serum on the second day of his illness. After two weeks at home following discharge he was again admitted on March 3, 1939, with Type 1 involvement of the right upper and middle lobes, and had an almost identical response to drug therapy, which was started on the third day of his illness. On each occasion his temperature dropped from over 104°F. to normal in nine hours. The second patient was a seventy-year-old man who entered the hospital on January 6, 1939, with a Type 1 pneumonia involving the right middle and lower lobes. Blood culture was negative. He received 140,000 units of serum, but his temperature rose steadily from 104 to 104.8°F. in the following three days. Sulfapyridine was then given, with a fall in temperature to 100°F. in the next eighteen hours, and subsequent recovery.

The only death in the drug-treated group occurred in a sixty-one-year-old man who entered the hospital on the fourth day of his disease with a Type 3 left lower lobar pneumonia. His blood culture was positive, and he was delirious on admission. His blood urea nitrogen was 132 mg. per 100 cc., and blood creatinine 6.5 mg. Despite administration of 20 gm. of sulfapyridine, oxygen and intravenous fluids his temperature gradually rose from 98 to 101.5°F. and he died on the fourth hospital day. Autopsy revealed almost complete consolidation of both lungs and granular contracted kidneys, which were thought to represent an old arteriosclerotic nephritis. A hypertrophied heart, generalized arteriosclerosis and syphilitic aortitis were also found.

The relative failure of the combined drug and serum therapy in the small group so treated is surprising, in view of experiments on their combined action both in vitro and in animals.[18, 19] Our figures are certainly too small to permit any conclusions on this point.

From our results it can be inferred that at least in the great majority of cases sulfapyridine exerts no serious toxic effects if used in the dosage described. However, nausea and vomiting were quite troublesome. The occurrence of both rash and drug fever in the 2 patients receiving over 40 gm. of the drug suggests that these large doses should be used with caution. We have observed no agranulocytosis or acute hemolytic anemia, but their known occurrence in occasional cases makes frequent blood counts and close observation essential.

We found sulfapyridine of particular value in cases first seen after the fifth day of the disease and in cases in which no type could be obtained. Seven cases falling in the first group and 9 in the second are present in this series, and all of them recovered. If any clear indication for the use of sulfapyridine exists it is in these groups.

SUMMARY AND CONCLUSIONS

The results in a series of 84 cases of lobar pneumonia are presented. Of these, 44 were treated with sulfapyridine alone, with only 1 death.

A smaller group of 22 patients treated with serum alone is included for comparison.

Sulfapyridine has been demonstrated to be an effective drug in the treatment of pneumococcal lobar pneumonia, and to be particularly applicable to certain types of cases. No serious toxic effects were noted in this series.

Ultimate evaluation of the relative effectiveness of serum and sulfapyridine in the treatment of lobar pneumonia cannot be made until a large number of cases have been recorded.

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GRANULOCYTOPENIA FOLLOWING SURGICAL SEPSIS AND TREATED WITH ADENINE SULFATE

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IT HAS been frequently observed that following operation many patients unexplainably become much sicker than the operation would warrant, whether owing to its extent or to the amount of infection present. These patients run a progressively downhill course without any distinct localizing symptoms and show progressive distention and general toxicity. Routine examination of the blood frequently shows the only abnormality to be a leukopenia with a normal differential but an increase in the percentage of young neutrophils. As Van Duyn[1] states: "This would indicate a wearing out of the leukopoietic power and offers an explanation of the patient's lack of response to ordinary measures." This leukocytic exhaustion always indicates a serious prognosis regardless of the initial pathologic lesion or operative manipulation.

Schilling[2] describes the successive steps in leukocytic exhaustion. First there is a leukocytosis with neutrophilia and an increase of young forms. With continued irritation the numbers of immature neutrophils become even more marked and myelocytes appear, and eventually the total count falls, with a resulting leukopenia and agranulocytosis. Schilling attributes this phenomenon to the overwhelming irritation of severe acute sepsis or to the persistent drain of a long-continued infection.

Agranulocytosis is considered by some authors[3] to be primarily a disease of the myeloblastic tissues followed by a loss of resistance resulting in overwhelming infection, the agent responsible for the cessation of myeloblastic activity being unknown. On the other hand, Reznikoff[4] believes that agranulocytosis as due to a depression of the production of granulocytes or to their delivery into the circulation because of an inherent failure on the part of the particular individual in the course of a toxemia rather than because of any toxic agent.

In view of the above, the following case of a patient with an apparently normal leukocytic reserve who developed a severe leukopenia and a rapid fall in the granulocytes, accompanied by a severe toxemia and prostration, in the course of an abdominal infection, is presented.

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CASE REPORT

B. H., a 40-year-old policeman, entered St. Vincent Hospital December 5, 1938, complaining of generalized abdominal pain with vomiting of 36 hours' duration. His past history was not significant other than that he had had a positive x-ray diagnosis of duodenal ulcer 15 years previously. He also had given fifteen blood transfusions in the past 2 years, the last one 10 days previous to the present illness. He had had no medication other than irregular use of Sippy powders and an irregular bland diet. He had been using no drugs and had been able to perform his regular duties.

Thirty-six hours before admission, while on duty, the patient complained of epigastric pain similar to the periodic attacks he had had for 15 years. The initial pain was relieved by drinking a glass of milk. One hour later the pain returned and was not influenced by a glass of milk or a Sippy powder. The following day the patient was quite comfortable until that evening, when a pain occurred in the lower abdomen, causing nausea and vomiting. When he was seen by his physician the pain was acute and diffuse over the entire abdomen and in the back, and radiated to the end of the penis. There was no frequency or dysuria. The pain was not controlled by ½ gr. of morphine, given in divided doses in 1 hour.

On admission the temperature was 101°F., the pulse 92, the white-cell count 16,900 with 86 per cent polymorphonuclears, the hemoglobin 75 per cent and the red-cell count 4,800,000. On local examination the abdomen was slightly distended below the umbilicus with generalized rigidity of the entire abdomen, more marked over the lower half. There was generalized tenderness in both inguinal regions. Deep palpation in the epigastrium caused pain. Rebound tenderness was referred to the lower abdomen and not well localized. There was marked suprapubic tenderness. Rectal examination showed no abnormal masses and no bulging, but there was slight tenderness anteriorly in the midline.

At operation on the day of admission a large amount of thin, turbid fluid was obtained. The appendix was retrocecal and perforated in its mid-portion over an incarcerated fecalith. The appendix was removed and the abdomen drained.

Following operation the patient's condition was fair until 2 days later, when there was an increase in abdominal distention with vomiting of retained gastric secretions, and restlessness and increased toxemia. This was accompanied by a fall in total granulocytes (Table 1). An Abbott tube with continuous suction was inserted, with only slight relief. The tube could not be inserted through the pylorus, presumably because of contraction due to the old ulcer, and was replaced with a Levine tube. Peristalsis was active and flatus and fecal return with the Harris drip were adequate, yet the patient became more toxic, restless and irrational, with increasing distention. One cubic centimeter of parenteral liver concentrate was given on the 2nd and 3rd postoperative days, without effect. The general condition grew worse, and

the polymorphonuclears continued to decrease. Ten cubic centimeters of Pentnucleotide was given on December 9, owing to delay in securing adenine sulfate. The same evening 2 gm. of adenine sulfate dissolved in 200 cc. saline was given intravenously. The following day the general condition was improved and the leukocyte count increased. This dose was repeated with an abrupt improvement of symptoms.

Five days later, on December 14, there was return of intense abdominal pain with increasing distention and rising temperature and pulse. Rectal examination was negative. However there was an adequate leukocytic response to the increasing infection. The white-cell count was 18,000, with 84 per cent polymorphonuclears. An enterostomy was performed, with prompt relief of the symptoms of obstruction. The skin irritation from profuse intestinal drainage following the removal of the enterostomy tube was satisfactorily controlled with daily exposures to infra-red and ultra-violet rays with kaolin dressings.

Following this the abdominal symptoms cleared up, to be followed by oliguria, with albumin, white and red blood cells, and hyalin and granular casts in the urine and a nonprotein nitrogen of 67 mg., a creatine of 3.3 mg. and chlorides of 250 mg. per 100 cc. of blood. This condition was gradually controlled, and the patient was discharged symptom-free on January 10, 1939. His abdomen was soft, his bowels were regular, and the enterostomy incision was almost completely healed. The blood chemical findings and counts were normal.

At examination on January 28 the patient was symptom-free and had gained weight, the bowels were regular, and the blood counts and differential count were normal.

TABLE 1. *Summary of Blood Counts.*

DATE	LEUKOCYTES	LEUKOCYTES						COMMENTS
	LEUKOCYTES	POLYMORPHONUCLEARS	LYMPHOCYTES	LARGE LYMPHOCYTES	EOSINOPHILS	ENDOTHELIALS	MYELOCYTES	
		%	%	%	%	%	%	
12/5/38	16,800	86	11	2	1			Operation: appendectomy
12/7/38	7,300							Liver concentrate, 2 cc.
12/8/38	4,200	33						Liver concentrate, 2 cc.
12/9/38	4,800	25	49	13	3	6	4	Pentnucleotide, 10 cc. Adenine sulfate, 2 gm.
12/10/38	7,400	47	42	0	5	4	6	Adenine sulfate, 2 gm.
12/12/38	12,800	70	25	3	1		1	
12/14/38	18,000	84	14	3	3			Enterostomy
1/10/39	8,200	62	27	6	1			

It was early apparent that the active process in this case was much more malignant than one of leukocyte exhaustion as described by Van Duyn,[1] because of the lack of response to liver therapy and the appearance of myelocytes in the peripheral circulation. It was evident that with the progressive failure and increasing toxemia a fatal agranulocytosis was inevitable.

From the considerable experimental work on agranulocytosis,[3-8] it has been demonstrated that nucleotides are a specific stimulus to myelopoiesis. If this is true, then when such stimulation is either lacking in the body or insufficient because of other destructive forces, the most effective therapy should include the attempted replacement of nucleotide in concentrated form.

The following conclusions from experimental work[8] place this therapy on a rational basis: (1) Nucleic acid exerts a chemotactic effect on normal myeloid foci, with a prompt effective increase in the delivery of granular leukocytes to the peripheral circulation. (2) Repeated large intravenous injections tend neither to exhaust nor to cause a malignant hyperplasia of the myeloid elements in normal animals. (3) A short course of injections stimulates a myeloid hyperplasia of normal marrow without otherwise injurious consequences, a fact which is reflected in an absolute and relative increase in the granulocytes in the blood stream.

Adenine sulfate prepared by the hydrolysis of yeast nucleic acid was chosen as the most effective agent. The material is prepared by dissolving the salt in normal saline, 1 gm. to 100 cc., by boiling, and is given intravenously. It is not readily soluble and it may be necessary to add 10 per cent hydrochloric acid to the suspension for complete solution. The latter mixture is slightly more irritating.

It is urged that a routine procedure in severe septic conditions consisting of initial complete blood counts on admission for comparison, and daily white-cell counts and differential smears, be made in order to determine early the presence of leukocytic exhaustion or granulocytopenia.

CONCLUSIONS

Granulocytopenia developing as a result of severe sepsis is a severe and fatal complication.

Nucleotides have chemotactic, maturative and initiatory stimuli for neutrophilic myelocytes when the basic mesenchymal tissues from which they arise are in a condition to respond.

Adenine sulfate in 2-gm. doses given intravenously is specific and non-toxic in stimulating myeloblastic activity under such conditions.

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REPORT ON MEDICAL PROGRESS

INDUSTRIAL MEDICINE

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INDUSTRIAL medicine is progressing along the lines of preventive medicine and the protection of the worker from the hazards of his environment. These hazards are the risks of accident and of occupational disease or poisoning. Naturally such risks occur in differing proportion, depending on the products manufactured and the processes employed.

In the majority of the large manufacturing plants machines are well guarded and workers are instructed concerning hidden dangers to be avoided, and are protected by engineering devices from exposure to noxious dusts and fumes. In addition, physical examinations on entrance prevent workers from being assigned to work for which they are unfitted, while periodic examinations of those exposed to hazard prevent the development of chronic poisoning among any having an idiosyncrasy to some particular substance. This control has been gradually developed over a period of years.

Industrial medical departments exist in few factories employing less than five hundred workers, in spite of the fact that nearly 62 per cent of the industrial wage-earners are employed in such plants.[1] The fact appears to be that while nearly 40 per cent of those working in factories have from fair to good medical supervision, the majority of the workers have only such supervision as is provided by the community physician, who, unless the worker is one of his private patients, only sees him following an industrial accident. In order to improve this situation the National Association of Manufacturers, through its Committee on Healthful Working Conditions, has started a campaign to inform small manufacturers of the value and importance of a simple, well-run industrial medical service, and to urge the establishment of such services throughout the country.[2] It is assumed that the physicians who are now employed to care for industrial accidents will be drawn more closely into contact with the factory and will have an opportunity to study the machine and other hazards to which the workers are exposed and to advise the management of steps which should be taken to remedy dangerous conditions.

The State of Massachusetts, through its Department of Occupational Hygiene, is prepared to help physicians taking over such work with advice and by examinations of the working conditions, maintaining secrecy as to the findings and the advice given. The American College of Surgeons is also glad to give what help it can in solving the problems that may be encountered, as is the American Medical Association.

The emphasis in industrial medicine is to prevent absence due to illness, whether of industrial or non-industrial origin, by every means it can, to reduce the period of incapacity from industrial accidents and to provide healthful working conditions for plant employees. Regarding the importance of non-industrial injury and illness it has been stated: "The average worker loses nearly nine days per year from non-industrial injury and illness or approximately fifteen times as much time as he does from industrial injuries."[3]

Surgery

Industrial surgery is chiefly traumatic surgery, and is carried out either in the factory dispensary in the case of minor injuries or in a general hospital in the case of major injuries. The majority of industrial injuries are minor in character and heal rapidly without loss of working time if properly treated. In a certain proportion of the cases the worker's task must be changed or modified in order that he may continue work. Continuing work is of great importance to him, as

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his earnings considerably exceed any compensation which he might receive, and his morale is maintained during treatment.

Gentle but scrupulous cleansing of all wounds, either with soap and water and alcohol or with benzine, followed by iodine or a 2 per cent solution of gentian violet, is all that is necessary for most minor lacerations. Sutures of lacerations when done are loosely tied to allow for subsequent swelling. In cases where there is the slightest chance of a severed tendon, careful tests of function are imperative. All crushing injuries, whether or not a fracture is present, should be splinted and x-rayed.

The difficult finger fractures involving the middle or the proximal phalanx can, after reduction, often be held in position by flexion of the fingers over a roller bandage instead of the cumbersome banjo or other traction splint, which should not be tried until the simpler method has failed. Fractures of a single toe or metatarsal will heal well and allow limited work if the foot is covered by a heavy wool sock and then immobilized in a United States Army type shoe.

Varicose veins are a frequent cause of disability because of the complicating ulcers and eczema. The present incision and injection method has produced normally functioning legs, and when it can be used is better than multiple injections.

There has been much discussion among industrial surgeons as to the value of the injection treatment of hernia. The general feeling appears to be well summed up by McMillan,[4] who after five years' experience believes: "This should not be looked on as a panacea, but in selected cases as an aid in attacking the problem of hernia and in other cases as a method which will afford help which cannot be obtained by any other procedure." Surgery still appears the best and most frequently employed method of treating hernias that develop among industrial workers.

Orthopedics

Of orthopedic conditions the "strained back" is of frequent occurrence. It varies from a minor pulling of the muscles and ligaments to a severe sprain. Any underlying disease prolongs the disability greatly, and there is a distinct psychological factor which must be combated.

Every workman who strains his back severely receives two injuries, one to his back, the other to his morale. Both conditions must be successfully treated in order to return the worker to his job. Irwig[5] reports that the deep injection of eucupine in oil produces a prolonged anesthesia in the painful back. The deep injection of novocain has been successful enough to suggest that this drug is worth trial. The conservative principles of rest and support are still followed in treatment of these cases.

Returning the patient to work requires the co-operation of his foreman. He should be given trivial work at first, such as running an elevator, and later work entailing only light lifting. The patient should be instructed to lift by bending his knees, keeping his back straight and using his thigh muscles in making the lift. He should be kept under medical supervision until able to resume his regular work.

Medicine

Among those practicing industrial medicine the emphasis has swung from the treatment of industrial accidents to the prevention, diagnosis and treatment of occupational disease. The importance of taking an occupational history in the case of every patient who works in industry is something the general practitioner in an industrial community should have in mind. "Such a history is especially important before an operation is decided upon, since unsuspected industrial disease may make such an operation unsafe at the time."[6]

Several diseases deserve particular mention.

Pneumoconiosis

Of the industrial diseases which are of fairly common occurrence the pneumoconioses are the most important. The present belief may be summed up as follows: only free silica (quartz) and asbestos can of themselves alone produce disease entities causing incapacity.[7] Other industrial dusts may result in the development of allergic symptoms among those exposed, as in the case of the castor bean, or may render the worker somewhat more susceptible to respiratory infections, as in the case of inert inorganic dusts, such as iron dust, cement dust and artificial abrasive dust. This belief is the result of much animal research and of clinical experience in Europe and America.

The three important factors which are considered in the case of a worker exposed to dust are the character of the dust, its quantity in the air breathed and the length of exposure.

The impinger described by the United States Public Health Service is at present the instrument most widely used to determine the dust count. Hatch[8] has suggested the following stand-

ards of permissible dust depending on the type encountered:

KIND OF DUST	MAXIMUM PERMISSIBLE CONCENTRATION *million particles per cu. ft.*
Containing no silica	50
Containing any small amount of silica, free or in combination	30
Containing 20 to 40 per cent free silica	10
Containing greater than 40 per cent free silica	5 (preferably less)

To this list should be added a permissible dust count of not over 5,000,000 particles per cubic foot of air for asbestos dust as recommended by the United States Public Health Service.[9]

The most important diagnostic evidence is secured by x-ray. In questionable cases it is agreed that stereoscopic and lateral views are necessary, and that interpretation of the x-ray films should be made by one having had considerable experience with this type of chest picture. The roentgenogram of a silicotic chest must show nodulation in both lungs, the nodules measuring from 4 to 6 mm., to be truly diagnostic of silicosis. In the late stage, where infection plays a part, conglomerate masses may involve the upper lobes of one or both lungs. These masses indicate tuberculosilicosis, and closely resemble the picture of chronic fibroid phthisis. The nodules tend to disappear, being obscured by the compensatory emphysema, which often involves the lower third of both lungs. Without nodulation or masses the diagnosis of silicosis should not be made. At Saranac, the term "stage of imagination" is used to describe certain x-ray photographs sent in with the tentative diagnosis of silicosis.[10]

Until 1938 the only possible means of protecting the worker were exhausts which removed the dust at its point of origin and specially designed respirators. Recent work at the Banting Institute[11] has suggested that the addition of 1 per cent metallic aluminum dust to the air exerts a neutralizing effect on silica dust through coating the particle with a film of aluminum hydroxide, thus converting it from a dangerous to an inert type of dust. Even if this is found to be the case, properly constructed dust exhausts will remain a better procedure.

The great danger in silicosis being the development of tuberculosis, it is considered a good practice to x-ray the chests of all workers who are to engage in dusty work, so as to ensure that they have no focus of tuberculosis which might be activated by free silica in the dust inhaled.

Asbestosis has been studied intensively. The diffuse interstitial fibrosis which causes such early dyspnea is now thought to be due more to the mechanical action of the asbestos fiber than to its chemical characteristics.[7] The so-called "curious bodies," otherwise known as asbestosis bodies, are found with enough frequency in the sputum of those not working in asbestos dust to make their presence alone of suggestive rather than of final diagnostic importance.[12, 13]

Both silicosis and asbestosis are characterized by dyspnea, occurring in the former usually in the late stage of the disease. The dyspnea of silicosis differs from that of cardiac disease in that the patient does not have orthopnea when lying down. A quick test of the extensiveness of the silicotic process consists in determining whether the patient can hold his breath for thirty seconds; the function of the lungs is not severely affected if this test can be successfully carried out. Cough is by no means invariable, and when present may disappear when the patient ceases to be exposed to dust.[14]

There are estimated to be about 600,000 workers exposed to free silica in the United States.[15] According to Bridge's[16] English records the duration of exposure before disability begins or a diagnosis is made varies from twenty-three to sixty years, with an average of thirty-five years, for silicosis, and from one to twenty-seven years, with an average of thirteen years, for asbestosis.

Cancer

The following rule suggested by Bridge and Henry[17] may well be used in deciding whether or not cancer is industrial in origin:

> The rate of incidence in the occupation under review should exceed that in the general population to a significant extent.
>
> In the occupation concerned there should be sufficient association of the worker with a substance proved experimentally to have carcinogenic properties.

Under this rule cancers of the lung occurring among workers exposed to silica and to asbestos dust are not industrial. Although they have been found at autopsy, the frequency does not appear as yet to be significant.[18]

The most interesting of the cancers in industry is that of the bladder, occurring among aniline dye workers. The trigone is the commonest site, but the tumors may appear anywhere on the bladder wall. The changes consist of congestion, telangiectasis and small areas of hemorrhage, followed by papillomas, which finally ulcerate. The interval of exposure varies from three to fifteen years. The dyes most frequently associated with the conditions are benzidine, betanaphthalamine and aniline. The method of their action is in doubt, and lies between their effect on the urine and their absorption by the blood.

The treatment at present is early removal or fulguration, followed by gold radon-seed implantation. This has not proved very satisfactory. Very high voltage x-ray treatment may prove more successful. At present it is in the experimental stage.

The connection between trauma and cancer has been discussed for years. Ewing[19] has set down the essential criteria as follows:

1. The authenticity and adequacy of the trauma. [It must be sufficient to produce alteration in the structure of tissue.]
2. The previous integrity of the wounded part. [The patient's word should not be wholly relied on.]
3. The tumor must arise at the point of injury.
4. A reasonable time limit must be observed between injury and the appearance of the tumor.
5. The positive diagnosis of the presence and nature of the tumor is essential.

According to Hoffman,[20] who quotes Ewing as above: "When the evidence shows that a wound of an apparently normal tissue never healed, that pain, swelling and discharge persisted for weeks and until the definite appearance of a malignant process, one must accept a presumption in favor of the traumatic origin."

Heat Cramps

The troublesome heat cramps often coupled with prostration which were formerly such a frequent cause of incapacity have been practically eliminated by providing 10-gr. tablets of sodium chloride near factory drinking fountains. The workers take from four to six of these tablets a day, thus replacing the salt lost by sweating. It is this salt loss which causes the symptoms, not the heat and the drinking of cold water.[21]

There is, however, a crucial danger zone of heat. Injuries to the health of workers begin to occur when work is carried out at a temperature of 90.5°F. or over, with a humidity of 90 per cent. At this danger zone the heart is accelerated, the body temperature rises and the body loses weight at a rate of 2 pounds per hour.[22]

Toxicology

In industry there are a large number of chemical substances in use whose fumes are toxic. The Division of Occupational Hygiene of the Department of Labor and Industries of Massachusetts[23] has drawn up a table of permissible concentrations in the workroom air according to the standards of the United States Public Health Service, several state commissions and other authorities. Fifty-eight dangerous substances appear on this list.

Most toxic substances used in industry are absorbed by the workers through the respiratory tract in the form of gases, fumes or dusts. The toxic effects, acute or chronic, are frequently bizarre and may suggest some non-industrial disease. Thus lead poisoning may simulate neuritis or rheumatism; poisoning by the chlorinated naphthalenes appears to be acute yellow atrophy of the liver or toxic jaundice; benzene poisoning resembles anemia or leukemia. The most important recent research has been applied to the chlorinated naphthalenes.

Chlorinated Naphthalenes

Three years ago there occurred in Massachusetts the death of 3 markedly jaundiced patients. These men were all workers in a factory where wire was dipped in a tank containing a solution of chlorinated naphthalenes. A careful investigation by the Division of Occupational Hygiene[24] suggested a toxic fume inhalation as the cause.

Research at the Harvard School of Public Health[25] showed that a destructive effect on the liver of experimental animals was caused by the inhalation of these fumes. The pathologic picture was one of necrosis and fatty degeneration of the liver cells. The toxic effects were similar to those found in the patients cited above.

Greenburg et al.[26] in New York reported 3 cases similar in type. Recently Drinker[27] has worked out a table of permissible concentrations of the vapors of fourteen chlorinated hydrocarbons for the air of workrooms. In the great majority the concentration is set as 0.5 mg. per cubic millimeter. In the same paper he shows that neither a high-calcium diet nor injections of xanthine, which have been considered as possible protectors, have any effect in preventing liver injury. Following the installation of suitable tanks with special exhausts, no further cases have developed.

A dermatitis resembling a heavy acne is frequently present among workers exposed to chlorinated naphthalenes.[26] It indicates that further exposure may lead to liver damage, and that the patient should seek other work and never return to a similar exposure.

Carbon-Monoxide Anoxemia

One of the common poisonous gases occurring in industry, to which the general population is often exposed, is carbon monoxide. The acute form of poisoning is well known, but the effects of chronic carbon-monoxide anoxemia are less well known and may suggest other diseases.

The two most frequent sources of this type of poisoning are defective gas heaters and automobile exhaust gases, the former being the more dangerous. The inhaled carbon monoxide, having an affinity for hemoglobin many times as great as that of oxygen, replaces the needed oxygen in the

red blood cell, smothering it. All the tissues of the body necessarily suffer from an oxygen deficit.

Individuals constantly exposed to carbon monoxide in small quantities gradually build up a resistance to the gas. This is apparently due to "the relation between the concentration of carbon monoxide breathed and the degree of saturation of the blood observed after repeated exposures."[28] Rapid concentration of carbon monoxide in the blood leads to symptoms of anoxemia, the symptoms usually beginning when the blood is 20 per cent saturated. Men breathing small amounts of carbon monoxide over a long period of time may not build up enough resistance and may develop symptoms of chronic poisoning. Here again, the effect of personal idiosyncrasy, which makes the diagnosis in industrial toxicology so difficult, plays an important part.

The commonest symptoms found by Mayers,[29] Beck[30] and others are headache and dizziness, gastrointestinal disturbances, drowsiness, faintness, weakness in the lower extremities, insomnia, cardiac disturbances and general neurological and mental symptoms. The symptoms, as one can see, are numerous, and usually several are grouped in each patient. Headache, nausea and weakness are the more frequent complaints. The anoxia of the red cells provokes pathologic changes in many organs.

> The possible pathologic changes due to chronic carbon-monoxide poisoning . . . in the nervous system may vary from damage to the lenticular nucleus and diffuse changes, such as are associated with a Parkinsonian syndrome or multiple sclerosis, to injuries to single nerves or sense organs. . . . A prolonged period characterized by cardiac symptoms may result in a certain degree of permanent enlargement of the heart and in myocarditis.[31]

It is therefore good practice in cases with complaints of a general nature in which there is pallor and the general picture is one of ill health to question the patient closely as to possible exposure to carbon-monoxide gas, either at his work or in his home.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 25331

PRESENTATION OF CASE

A fifty-five-year-old white married man was admitted complaining of blindness.

Fifteen years prior to admission he had a "cyst" removed from his right lower leg. A mass which was painful to pressure grew back in its place. It was not attached to the skin or to the underlying bone. The appearance of this mass was followed by others all over the body, some of which by the time of entry had attained rather large size. Eighteen months before admission the patient first noticed stiffness of his neck and soreness associated with movement. This had gradually increased up to the time of admission. Three months later members of his family saw him fall out of a chair. They discovered that this fall was due to muscular weakness. At the same time they noted a left facial paralysis and believed that he had suffered a stroke. However, the condition did not clear up. Six weeks before entry the patient noticed the onset of double vision and blurring of vision. He said that his left eye was affected first but was not certain of this. He then became progressively blinder until at entry he could see nothing. There was no headache, nausea, vomiting, difficulty in swallowing or difficulty in speaking. Two years before admission he had had tinnitus in his right ear for about one month. There was no tinnitus or vertigo on entry. He had not had disturbance of sphincter control. His past history and family history were noncontributory.

Physical examination showed an emaciated man who appeared to be older than his stated age. There were multiple nodules over the body varying in size from 1 to 10 cm. in diameter. They were characteristically firm to hard, not attached to the overlying skin or fixed to the deeper tissues. Where present near large muscles they seemed to be an integral part of the muscles, yet formed discrete masses which could be differentiated from the remainder of the area. They were present on the scalp, right abdomen, right thigh, right lower leg, right groin and left supraclavicular area. Examination of the heart revealed occasional extrasystoles. The blood pressure was 192 systolic, 135 diastolic. The lungs were normal. A small firm mass was present in the right lobe of the prostate. Neurological examination showed a well-oriented man whose memory was rather hazy. Both fundi showed choked disks. There was a complete loss of vision in both eyes. Both pupils reacted to light and accommodation. External ocular movements were normal. The corneal reflexes were present. There was a complete left facial weakness. The Weber test was positive to the left, the Rinne negative on the left, positive on the right. The right palate was down, and the palate moved to the right. Swallowing and speaking were normal. Movements of the neck and shoulders were weak. The tongue protruded to the right with fibrillation and some atrophy. The finger-to-nose test was fairly good, heel-to-shin poor. There was no adiadokokinesia. The left leg showed atrophy and emaciation of all muscles, with fibrillation. Strength was poor in all muscles especially in the legs. Neck movements caused pain in the back of the neck. The upper extremities showed weakness with no definite lateral localization. The knee jerks were increased, more on the right than left. Both ankle jerks were present, with sustained clonus which spread to the entire leg. The Babinski, Oppenheim, Gordon and Chaddock signs were bilaterally positive, more marked on the left. There was hypesthesia to pain and temperature over the entire right leg to the hip. Vibration sense was poor on the right leg. Position sense was lost in both feet.

The temperature was 98°F., the pulse 78, and the respirations 15.

Examination of the urine was negative. The blood showed a red-cell count of 4,530,000 with 70 per cent hemoglobin, and a white-cell count of 7100 with 65 per cent polymorphonuclears. A blood Hinton test was negative. A lumbar puncture was done, but the dynamics were not entirely satisfactory because of pain and poor co-operation. The initial pressure was 350 mm. of water, with the combined jugular pressure 450 mm. and the final pressure after removal of 10 cc. of fluid 180 mm. The fluid was slightly yellow. There were 10 lymphocytes per cubic millimeter. The total protein was 105 mg. per 100 cc., the sugar 78 mg. and the gold-sol test 0001210000. A spinal-fluid Wassermann test was negative. A stool examination was guaiac negative. An electroencephalogram showed abnormal waves and was thought to be suggestive of more than one lesion or a diffuse process.

X-ray films of the chest showed a round area of increased density measuring 2 cm. in diameter close to the right lateral chest wall and another measuring 4 cm. in diameter close to the right border of the heart in the right lower lung field.

There was another 3-cm. area in the left apical area. There was marked arteriosclerosis in the aorta. The heart was not remarkable. Examination of the skull was hampered by opisthotonos. There was marked vascularization of the skull without other evidence of abnormality. The cervical spine showed a slight degenerative change between the sixth and seventh vertebrae without other evidence of abnormality. Films of the right leg showed an area of calcification in the soft tissues of the right calf lateral to and slightly in front of the fibula. The calcification had a lace-like structure, and there was definite evidence of shell-like calcification in the process. There was a soft-tissue mass bulging into the subcutaneous fat. The mass overlay the bone. There was no definite evidence of bone involvement. Stereoscopic films of the leg showed the calcification to lie essentially at the periphery of the soft-tissue mass. Repeat x-ray films of the chest three days later showed the three round areas of consolidation in the right lower portion of the lung and in the left apex to be unchanged. The one in the lateral portion of the right lung was situated close to the chest wall. The second had a semicircular shape, was close to the heart but distant from the chest wall. The third in the left apex was near the anterior chest wall, probably not in contact with it.

A biopsy of the mass in the right groin showed a soft, gray and yellow, fatty, apparently somewhat cystic mass. On microscopic examination, members of the pathology department were not in agreement as to whether the tumor was malignant but believed that it was of neurogenic origin.

On the fourteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Edward D. Churchill: I am going to assume the present illness began eighteen months prior to admission. Statements before that time are vague in relation to when these masses appeared and also in relation to their size, which is merely recorded as "rather large."

The symptoms that are commonly looked for in increased intracranial pressure were absent. The record states: "The right palate was down." I am puzzled by that statement because I thought that when the palate was down it meant paralysis, yet the next note indicates that the palate moved to the right.

I take it we have a patient with spastic paralysis and a lesion above the cortical spinal tract. I am entirely confused by the array of neurological signs and symptoms, and I shall have to turn to someone else for help about them.

In commenting on the encephalogram they say: "The record suggested more than one lesion or diffuse involvement." That is more or less the conclusion that I came to on reading the physical examination.

I should like to ask either Dr. Ayer or Dr. Kubik, whichever one has not seen the patient, if, first of all, on the basis of this evidence we could safely interpret the loss of vision associated with the choked disks as generalized intracranial pressure; and, further, whether there are any localizing signs that would enable us to state that this is a single lesion within the cranium, or if we have evidence that there are multiple lesions.

Dr. James B. Ayer: A single intracranial lesion of expanding type could cause all the symptoms and signs here shown, especially if placed in the posterior cranial fossa. A single tumor here placed often gives bilateral spasticity in the extremities from direct pressure on the brain stem, together with choked disks from occlusion of the aqueduct of Sylvius. However, only long-standing choked disk causes complete blindness, and we may well suspect that some direct pressure on the optic pathways was also present, indicating multiple tumors. There may also be a tumor of the cord, which after all is the commonest explanation of bilateral paralysis of the extremities.

Dr. Churchill: Then we come to the question of speculating as to what type of tumor or tumors might produce the picture. As we started with the description of the lesion of course we thought of multiple neurofibromas. However, neurofibromas in their multiple form — or von Recklinghausen's syndrome — arise from the sheaths of the terminal cutaneous nerves. If I remember my teaching correctly they are never intracranial. They might grow by extension through a vertebral foramen and cause pressure on the cord, the dumbbell type of tumor; but I do not expect them to occur within the cranium and be responsible for increased intracranial pressure. Again, a peripheral neurofibroma is in the skin, not beneath the skin. It may stick out a bit but recedes into the skin as it is pressed. In their multiple form they are also apt to be associated with pigmentation and cutaneous tabs. Of course multiple neurofibromas may occur along the nerve trunks. When they are multiple they are usually associated with smaller tumors in the skin.

What other type of tumor may present this picture? I am rather at a loss to know unless I enter the very dangerous ground, dangerous pathologically and clinically, of a miscellaneous group of tumors known as endotheliomas or peritheliomas. Just what is their present status in tumor pathol-

ogy, I do not know. I am not aware as to whether they have all been discarded, or whether they are still recognized. There are several interesting aspects of the tumors of this patient that would make them fit into the descriptions of endotheliomas or peritheliomas: they are multiple; they are slowly progressive; they occur in the dura or in the pia; they may calcify; they may be confused with neurofibromas on microscopic examination. In the chest we notice that the tumors are all located in proximity to the pleura. In the extremities, if we make the diagnosis of endothelioma, they can arise from the perivascular nerves.

Other types of neoplasm may be excluded. There is a little clue in the prostate. There was a hard mass in the right lobe, but that is a common finding and always invokes a long argument; there is no further evidence about it. It apparently did not arouse suspicion, so that we have no expert advice on how it felt or whether it could be a primary focus.

In conclusion, I shall let the matter rest and make a guess that we are going to find multiple tumors involving the meninges, the dura, the pleura and the peripheral nerves, and that the pathologist may still be working to classify this tumor to keep from throwing it into this rather hodge-podge discard of the so-called endotheliomas or peritheliomas.

Dr. Ayer: I should disagree with Dr. Churchill's conclusions that neurofibromas do not occur intracranially. They may be present wherever fibroblastic tissue occurs, as in the eighth cranial nerve, and neurofibroma of the acoustic nerve is relatively common. With acoustic symptoms so prominent I should favor the presence of an acoustic neuroma, with perhaps other intracranial neuromas, associated with the general picture of peripheral neurofibromatosis. The pathological types vary in different locations, and even vary in the same individual in point of time so that all the tumors found peripheral or central fail to present the same degree of malignancy. This aspect I prefer to leave to the pathologist.

Clinical Diagnosis

Multiple neurofibromas.

Dr. Churchill's Diagnosis

Multiple endotheliomas or peritheliomas.

Anatomical Diagnoses

Multiple neurofibromas (von Recklinghausen's disease), subcutaneous, retroperitoneal, thoracic, cerebral and spinal.
Bronchopneumonia, bilateral.
Arteriosclerosis, slight, aortic and coronary.
Operative wounds: biopsy of tumor of leg, craniotomy, ventriculotomy.

Pathological Discussion

Dr. Tracy B. Mallory: I became interested in the clinical picture in this case because I was asked for some advice following the first biopsy and before the cerebral operation. As is stated in the record, there was some difference of opinion among the various members of the laboratory staff who examined the biopsy specimen as to whether this lesion in the leg was benign or a fibrosarcoma and hence capable of metastasis. We frequently meet borderline degrees of malignancy where a positive decision cannot be rendered on purely histological grounds. I felt rather strongly that one had to assume in this patient that we were dealing with multiple tumors rather than metastases from a single tumor, and that the patient ought to be given the benefit of cerebral exploration since intracranial neurofibromas are among the few benign cerebral neoplasms and the results of operation are usually excellent. Dr. Kubik will tell us about that when he describes the findings in the brain. If the operation had been done a year earlier instead of in a nearly moribund patient it would almost certainly have been at least temporarily successful.

The rest of the autopsy showed multiple tumors in various soft tissues scattered through the extremities; there were a great many tumors within the pelvis and along the posterior wall of the abdominal cavity, almost all intimately associated with the nerves running down in that region. It was rather difficult in most instances to say whether the tumors were attached to nerves. In two or three instances, however, such attachment could be proved. The various chest masses were all outside the lungs. One was on the lateral surface of the pericardium in apposition with the phrenic nerve. One overlay an intercostal space in contact with the intercostal nerve. The third had extended down from the neck where it lay in close contact with the sympathetic chain. There were no tumors within the lung itself.

Dr. Charles S. Kubik: At operation it proved possible to resect only a portion of the tumor. The patient developed pneumonia postoperatively and died in three days. The tumor was rather large, about 4 cm. in diameter, and situated in the left pontocerebellar angle. It was not quite clear from just what nerve root the tumor came. It was thought at autopsy that it did not originate from the acoustic nerve but from one of the nerves that entered the jugular foramen. It was somewhat different from the usual tumor of the nerve

sheath found in this location in that it was a little more diffuse, displaced the brain stem more and was quite definitely adherent to the leptomeninges. It did not infiltrate the substance of the brain stem. It contained a number of cysts. Histologically it has the appearance of an acoustic or other benign nerve-sheath tumor, and the microscopical findings would have led me to call it perineurial fibroblastoma.

There are differences of opinion as to the origin of tumors of this type. Some believe that they arise from the cells of the sheath of Schwann, others that they come from the mesodermal perineurial sheath. Some would have it that in von Recklinghausen's disease it is the sheath of Schwann while in cases of solitary tumors it is the perineurial sheath. These differences of opinion have produced a variety of names, neurofibroma, perineurial fibroblastoma, Schwannoma and neurinoma being the commonest.

DR. MALLORY: Dr. Churchill has given us the classical description of von Recklinghausen's disease, but the present-day tendency, I think, is to broaden the syndrome a good deal and to include in it all cases of multiple tumors of nerves. An effort has been made, as Dr. Kubik has explained, to classify these tumors into two types. We have found this impractical because of the frequency of transitional forms. Moreover, in a single case of von Recklinghausen's disease we have seen classical examples of both types. Therefore we believe that the distinction is not important.

DR. AYER: Was there only one cerebral tumor? And was the cord examined?

DR. MALLORY: The cerebral lesion was single, but there was a tumor of one of the upper cervical nerve roots which had partially destroyed the axis. This might well have eventually become a fatal lesion if he had survived the cranial exploration.

CASE 25332

PRESENTATION OF CASE

A five-year-old American girl was admitted with the complaint of constipation of one week's duration.

The child was delivered with the aid of forceps at full term. The birth weight was 8 pounds. Because of difficulty in nursing, a formula was substituted which included orange juice and cod-liver oil. There were no childhood diseases, and she had not been vaccinated or immunized against diphtheria. She failed to walk or talk until the age of three. It was stated by the mother that the child had always had a large abdomen and had continually been constipated, so that frequent, sometimes daily, enemas were necessary to produce evacuations which at best were always poor. The child was unable to control the passage of urine.

Two weeks before admission the patient complained of abdominal pain and discomfort, and her abdomen seemed gradually to enlarge. Three days passed without a bowel movement, and enemas were not productive. One week before entry returns from enemas were "like hard stony pebbles, brown in color, without blood, pus or mucus." She began to vomit food, and seemed to pass flatus per anum. For three or four days before entry the child appeared "feverish," although the temperature was never actually taken. Mineral oil was administered for two days, with but scant evacuations.

The physical examination revealed a fairly well-nourished girl with typical Mongoloid facies and a markedly protuberant abdomen. There was a slight cyanotic tinge over the extremities. The fontanelles were closed. The palpebral fissures of both eyes were narrowed. The teeth were markedly carious, and the tonsils and pharynx slightly injected. In the neck there were a few small nontender cervical nodes. Examination of the heart and lungs was negative. The abdomen was symmetrical but markedly protuberant and tympanitic. There was an eventration of the umbilicus. No organs or masses were palpable, and there was no spasm or tenderness. A small hard mass located at the junction of the metacarpophalangeal joint of the left hand was thought by the examiner to be evidence of an extra phalanx previously removed. The rectum was dilated, empty in its lower portions, but filled higher up with soft, brown feces.

The temperature was 100°F., the pulse 80, and the respirations 24.

Examination of the urine was negative. The blood examination showed a red-cell count of 3,200,000 with 65 per cent hemoglobin (Sahli), and a white-cell count of 19,600 with 80 per cent polymorphonuclears. The blood smear was negative. The vomitus was black and coffee-grounds in appearance, with a fecal odor, and gave a 4+ guaiac test. A blood culture was negative, the carbon-dioxide combining power 12.2 cc. of N/10 H_2CO_3 per cent, and the chlorides 102.5 milliequivalents.

X-ray examination showed a markedly distended abdomen. The diaphragm was high in position. The abdomen was filled with a large colon distended by air and feces. The visible distention involved particularly the sigmoid but also the descending and transverse colons, with the latter overlying the liver and reaching as high as the diaphragm. Films of the forearm, tibia, fibula

and lower end of the femur on each side showed no evidence of disease.

On the third hospital day the patient received a 500 cc. barium enema, none of which was expelled. During the evening following the procedure about 200 cc. of barium was removed by constant suction. The stool was pink in color and gave a 4+ guaiac reaction, though no red cells were seen. The next day she was given spinal anesthesia, and about ten minutes following this a moderate amount of gas was passed per rectum. About fifteen minutes later a peristaltic pattern was visible over the abdomen. Fluoroscopic examination twenty-five minutes following the anesthetic showed no remarkable change in the size of the colon or in the amount of barium present. Throughout the entire procedure the patient displayed no untoward reaction; her general condition remained the same. Wangensteen drainage and rectal suction were instituted, and a small transfusion was given. The next day, in spite of all therapeutic measures, the temperature, pulse and respirations rose rather precipitously and she died on the evening of the sixth hospital day.

Differential Diagnosis

Dr. John Stewart: Perhaps some of the radiologists will comment on this film, but the description as given sounds adequate. We see a hugely dilated colon with an elevated diaphragm. I do not see any loop of small bowel, and apparently only the colon was dilated.

It seems that there are two central features in the clinical picture: mental deficiency and abdominal enlargement. These two findings may or may not be related. Whenever we see a child with mental retardation and abdominal enlargement we naturally think of the possibility of cretinism, but there seems to be very little evidence to support such a diagnosis in this case. The x-ray appearance of the bones apparently is normal. There had been no failure in closure of the fontanelles, and other points in the physical examination are not consistent with a diagnosis of cretinism. Therefore, we are confronted with the problem of determining the cause of abdominal enlargement in a child who obviously was a Mongolian imbecile. Presumably the mental retardation was due altogether to the Mongolism.

Abdominal enlargement in a child must always suggest the possibility of tuberculous peritonitis. This disease presents a varied picture, just as the lesion is varied, and it may run a protracted course. In this particular case, however, there were no palpable abdominal masses which might be inflammatory products of the tuberculosis. There was no evidence of ascites and, further, the x-ray films show that the abdominal enlargement was due to a dilated colon. Therefore, it is not necessary to suppose the enlargement of the abdomen came from peritoneal exudate or masses. The results of the tuberculin test are not given. Such information might be of value in a child of this age, but on the whole I see very little on which to make a diagnosis of tuberculous peritonitis.

The problem then reduces itself to consideration of causes of megacolon in a Mongolian imbecile. The three possibilities which occur to me are: celiac disease, chronic intestinal obstruction from some definite organic lesion, and Hirschsprung's disease or idiopathic dilatation of the colon. I suspect that the dilatation of the colon had been present since early infancy. I should not want to attempt to discuss celiac disease authoritatively for you, but it seems to me that in this case there was a good deal of evidence against such a diagnosis, including the absence of the typical fatty or fermentation stools, the fairly good nutrition that this patient showed and the lack of any chronic disturbance in calcium or phosphorus metabolism as shown by the normal appearance of the bones in the x-ray films. The character of the stools is an important point in excluding the diagnosis of celiac disease in this case. Chronic obstruction of the large bowel from a definite organic lesion, such as a mucosal diaphragm in the region of the rectosigmoid, cannot be excluded, but there is good reason to suppose that there was no such organic obstruction in this case. There had been an absence of bouts of abdominal pain and vomiting prior to the present illness. The x-ray study of the colon would tend to exclude the presence of a definite obstructing lesion at the rectosigmoid, although this region is difficult to visualize in the colon, particularly in the presence of a redundant dilated colon. That leaves us with the diagnoses of Hirschsprung's disease and Mongolism.

Then the question of the explanation of the terminal illness comes up. Two complications that are apt to be encountered in a case with a dilated stagnant colon, namely acute obstruction, as from volvulus, and infection and ulceration in the colon. I see very little to suggest the former in this case. The duration of the present illness and the x-ray studies tend to exclude volvulus. However, I do think it quite likely that the patient developed infection and ulceration, and very likely perforation, in the dilated colon.

If there was perforation of an ulcer at what time did it take place? The symptoms of the present illness proper, with increasing abdominal enlargement, increasing constipation and abdom-

inal pain, fever and the vomiting of material which had a fecal odor and a positive guaiac reaction, might depend on the development of a local peritonitis about a perforation, perhaps two weeks before admission. Then we should have to suppose that diffuse peritonitis developed in the hospital while the patient was under study, and my guess would be that such was the case. Whether or not there was a terminal pneumonia, I am unable to say on the insufficient evidence that is submitted. However, I should say that this was Hirschsprung's disease in a Mongolian idiot, that infection and ulceration of the colon eventually developed and that death came about from perforation and peritonitis.

Dr. Harold L. Higgins: I should like to ask Dr. Stewart what he thinks about the giving of the barium enemas and the significance of no shrinking in the size of the colon following spinal anesthesia.

Dr. Stewart: Spinal anesthesia was given, of course, as a test to determine whether there was an autonomic imbalance. It sounds to me as if the test in this case was rather equivocal. There was some appearance of a visible peristaltic pattern afterward, but on the other hand there was no x-ray evidence of shrinkage of the colon. I do not believe the results help me one way or the other in the diagnosis of this case.

Dr. Arthur W. Allen: Do you lay any stress on the urinary incontinence in association with the megacolon?

Dr. Stewart: I had attributed that to the mental deficiency, but of course the presence of an intrinsic lesion in the cord which might disturb both bladder and bowel function would have to be considered. But it does not seem to me that we have any supporting neurological evidence on which to make such a diagnosis.

Dr. Richard S. Eustis: Do you think that fecal impaction following constipation which is so common in Mongolian idiots could have produced the obstruction? I think of Mongolian idiots as thoroughly constipated, feeble-minded children, and here is a rather neglected child who had lived on enemas. The stools are described as small hard pebbles. Why did she not have a fecal impaction above the region they cleared up with the enemas before they gave the barium?

Dr. Stewart: It seems entirely possible that she might have had fecal impaction, but I see no diagnostic value in that point, inasmuch as she might have had it with a dilated colon from any cause. Also the question might come up as to whether there was any relation between the mental deficiency and the development of megacolon. At previous conferences Dr. Mallory has dealt with that question in adults. The inmates of insane asylums, for example, occasionally have megacolons without any disease of the spinal cord, I believe.

Dr. Henry H. Faxon: Do you not think it is surprising that the vomitus was black with a fecal odor and gave a 4+ guaiac test on the basis of your explanation of the picture?

Dr. Stewart: Yes, it is. I do not see why there should be such a free movement of the intestinal stream in the reverse direction, but I assume that the blood was due to ulceration of the colon.

Dr. Robert Linton: I saw this patient on the wards and was partly instrumental in having barium enemas and spinal anesthesia given. I do not believe that everything is known about megacolon that one would like to know. There are two types, the congenital and the acquired. This child was given spinal anesthesia in an attempt to see whether with release of the sympathetic innervation we could get emptying of the colon; it reached to the nipple line and that theoretically should anesthetize the lumbar ganglia and splanchnic nerves. The operation considered best at present for the relief of megacolon removes these nerves. In this case the spinal anesthesia failed to contract the bowel, but I do not believe that ruled out the sympathetic system. I think the patient was so ill and had been sick so long that the colon just could not respond.

Dr. Higgins: In connection with the question Dr. Stewart raised as to the differential diagnosis of celiac disease and Hirschsprung's disease, I may comment that in celiac disease the abdomen shows marked and rapid variations in size. It may be very small in the morning and very large in the evening. In Hirschsprung's disease it tends to enlarge gradually until an evacuation occurs. In making the differential diagnosis, we measure the abdomen twice a day.

The child's being a Mongolian idiot probably has a bearing on the death. A Mongolian idiot has notably poor constitutional resistance, and a relatively minor intestinal disturbance or infection may prove fatal. I think that death was quicker in this case for that reason. The Mongolian idiot usually has poor muscular tone; I wonder if perhaps the muscular tone might have affected the smooth muscle of the intestine as well as the skeletal muscle. However, one of the doctors at the Wrentham State School has told me that in their experience megalocolon and Mongolian deficiency had not occurred together.

The child's temperature was fairly normal until about eight hours before death, when it rapidly went up to 106°F. The child was having a varied blood pressure, ranging from 70 to 100 sys-

tolic. The last recording before death was 70; it seemed that a certain amount of medullary reaction with low blood pressure, poor circulation and a high temperature played some role in the immediate cause of death.

Clinical Diagnoses

Megacolon.
Intestinal obstruction with toxemia.
Peritonitis.
Mongolism.
Polydactylism.

Dr. Stewart's Diagnoses

Hirschsprung's disease.
Mongolism.
Colonic ulceration with perforation and peritonitis.

Anatomical Diagnoses

Congenital megacolon (Hirschsprung's disease).
Multiple ulcerations of colon.
Mongolism.
Polydactylism.
Atrophic thymus.

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy showed a large megacolon. In addition there was incomplete rotation of the intestinal tract, so that the cecum was not in the usual place, and had not progressed any farther around than the right upper quadrant. The peritoneal cavity was perfectly clean. There had been no perforation. On the other hand the mucosal surface of the colon showed numerous ulcerations. These were not very deep and did not seem very significant to us. There was no pneumonia. We found nothing except these rather recent looking ulcers in the colon that would explain the fever. The autopsy was limited so that we did not have a chance to examine the pituitary gland or various other things that might be of interest to look at in a Mongoloid. We did make as careful an examination as we could to rule out spina bifida, and could not find it.

Dr. Stewart: Were there any definite lesions in the region of the left colon? Any obstruction?

Dr. Mallory: No.

Dr. Eustis: Was the colon empty or full?

Dr. Mallory: Moderately full.

Dr. Eustis: Enough to cause obstruction and the vomiting of coffee-grounds material?

Dr. Mallory: I do not know. I should not want to say it was any fuller than it had been for two weeks. It certainly was still very full.

Dr. Margaret M. Glendy: Were the suprarenal glands all right?

Dr. Mallory: Yes. The only endocrine gland in which we noted any abnormality was the thymus, which seemed atrophic.

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THE APPROVING AUTHORITY

With the action of the Senate giving Senate Bill 395 leave to withdraw, there comes to an end, for the time being, legislative discussion concerning the scope of the jurisdiction of the Approving Authority of Massachusetts for colleges and medical schools. The Authority was created by statute in 1936, the effective date of which was originally set at January 1, 1939. Bitter opposition on the part of some medical schools having been ineffective against the increasing popular demand for control of such institutions, a deferring of the effective date for three years more was sought, ostensibly for the purpose of enabling the inferior schools to meet the presumably reasonable demands of the Authority. Only two years were granted, but the prophecy of some of the protesters against extension has been fulfilled; namely, that the added time would be used in further attempts to make the Authority of no effect, instead of improving the schools. This has been shown by the subsequent bills which have been introduced but which were not passed. Many legislators have thought that the Authority, once created, should be given the opportunity to show what it could and would do before attempting to abrogate its powers.

It is not necessary to discuss the bills in detail, suffice it to say that they were worded in such a way that even some of the keenest legislators were deceived, for they regarded the bills as perhaps unnecessary but quite harmless. Who could object to a law which required that all examinations should be fair and just? But on some other words not only was no emphasis laid, but attention was distracted from them, often by misstatements of fact.

Too little has been said about the Approving Authority and about the significance of its creation, which was an epoch-marking event for Massachusetts. Naturally, with the effective date set so far in the future, the Authority has had little to say for itself, and except for a general statement of certain requirements called for by the statute, has, to the best of our knowledge, made no decision of public record concerning medical schools. The critical decisions by the Board of Registration in Medicine, namely rejection of candidates for examination on the ground that they are graduates of schools not approved by the Authority, are not likely to be made until 1945, when the first candidates admitted to medical school after January 1, 1941, receive their degrees and make application to the Board.

Reference has been made to the significance of the act creating the Authority. It represents a new attitude on the part of the Commonwealth toward medical schools. There is recognition that a medical school is a quasi-public institution, with responsibilities not merely to those who control it and to its customers, but also to the public, with whom its former customers are to traffic for their health and their lives. Only a governmental agency, under statutory direction, can effectively

see to it that such an institution properly discharges its responsibilities.

Another significant feature of the new legislation, which some have considered of greatest importance, is the introduction of the Department of Education into the evaluating body. It is true that the Commonwealth maintains no medical schools, but colleges giving the required premedical education are also to be subjected to scrutiny and for this function the commissioner of education should be well qualified.

It is well indeed that the health of the people of Massachusetts should have better protection. It is especially a matter for satisfaction that machinery has been created and set in motion to give as much health protection through the practice of medicine as exists in any other state. Too long has Massachusetts been truly designated as a "dumping ground" for physicians of poor grade. Reports from the Board of Registration in Medicine indicate that at least half the candidates they must examine would not be admitted to examination in any other state. No wonder that no other state will reciprocate with Massachusetts in regard to licenses to practice medicine.

The task before the Approving Authority seems rather simple, though unexpected difficulties may later come to the surface. Undoubtedly so long as it is possible to make money by giving a medical education, efforts will be made to repeal or nullify the Massachusetts law, but no state that we know of has recalled such approving authority, once given. We await with interest reports of the activity of the Approving Authority of Massachusetts.

LOOK BEFORE YOU LEAP

THE water hazard — the danger of deaths from drowning — has always been recognized as one of our summer liabilities, but a liability that can conceivably be greatly mitigated, when suitable educational forces are put to work. Swimming instruction, made universally available and begun at an early age, will be the most important of these forces; in addition to this, the proper type of publicity to awaken intelligent water consciousness will have its desired effect.

The Metropolitan Life Insurance Company, however, in its *Statistical Bulletin* for June, mentions another definite water hazard to which swimmers, rather than non-swimmers, are exposed, and which is ordinarily unassociated with the danger of drowning. This is the liability of serious injury from diving accidents, which result in at least two hundred deaths annually in the United States — practically all due to neglect of the simplest principles of caution.

Analyzing the mortality records of one hundred policyholders who were killed in diving accidents, it was found that 68 per cent died mainly because they failed to investigate the depth of the water or to estimate correctly the depth needed for a safe dive. Most of these dives resulted in broken necks. Frequently the victim had never before swum in the body of water in which he lost his life; some failed to take into account the difference in tides; others dove from boats that had drifted into shallow water.

The next 18 per cent struck against submerged objects, usually rocks, in water which the diver had failed to examine before his plunge. In the remaining 14 per cent certain other forms of carelessness were responsible for the fatal accident: two persons diving simultaneously and striking their heads under water; striking a previous diver who had not been given enough time to emerge; striking the water flat during a high dive; diving too close to a dock guard at a pier and striking it; striking the head against the side of a swimming pool; diving from the back of a friend into breakers.

The conclusion is so obvious that no moral need be pointed out. It is a simple matter of looking before leaping.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

INVERSION OF THE UTERUS OF TEN WEEKS' DURATION

Mrs. M. B., a thirty-year-old woman, was admitted to the hospital ten weeks post partum on May 25, 1938, with a tentative diagnosis of subinvolution of the uterus. For seven weeks following the delivery of her second child there had been a persistent brownish vaginal discharge with occasional small amounts of bright-red blood. Then there had occurred intermittent painless vaginal hemorrhages of moderately large amounts, particularly when at stool, with large clots forming between the episodes of gross hemorrhage.

The patient's past history, family history and recent systemic history were all essentially negative. Catamenia began at fourteen, were regular with a twenty-eight-day cycle and lasted four days without pain. Her first baby had been delivered in another city by forceps and episiotomy following a long, hard labor. The puerperium was said to have been normal. Her second baby was delivered on March 17, 1938, the delivery and puerperium having been normal, except as noted above.

On admission the patient's general condition was fairly good. There was a paleness of skin and mucous membranes. The red-blood-cell count was 2,770,000 with a hemoglobin of 45 per cent. The blood pressure was 148 systolic, 96 diastolic. Abdominal examination was negative except for a slight amount of lower abdominal spasm. The vagina was filled with clots and examination disclosed a total inversion of the uterus. An iodoform pack was inserted to control bleeding.

The following day a transfusion of 500 cc. of citrated blood was given, bringing the red-cell count to 3,050,000 and the hemoglobin to 55 per cent.

On the second day following admission, under spinal novocain-pontocaine anesthesia, a Spinelli operation was performed. The uterus was exposed per vaginam, the anterior cul-de-sac opened, the anterior cervical ring cut and the incision extended along the anterior surface of the uterus up to the fundus. The uterus was then reverted and the uterine incision sutured. Soft-rubber T tubes were inserted into the anterior and posterior cul-de-sacs for drainage. A self-retaining catheter was inserted, and iodoform gauze packed in the vagina. Five hundred cubic centimeters of citrated blood was given immediately after the operation. The patient left the operating room in good condition.

The postoperative course was essentially uneventful. There was a slight degree of abdominal distention, which cleared up in a few days. The iodoform vaginal pack was removed on the second postoperative day. By the tenth postoperative day the red-cell count was 3,640,000, and the hemoglobin 60 per cent. The patient left the hospital on June 11, fifteen days after admission.

Comment. In this case, indifference on the part of the patient or attending physician or both allowed the condition of repeated small hemorrhages to continue for seven weeks without an adequate diagnosis. A red-cell count of 2,770,000 and a hemoglobin of 45 per cent are indicative of the amount of blood gradually lost. Continued bleeding during the puerperium demands vaginal examination. The transfusion preceding operation, after a vaginal examination had disclosed the true diagnosis, was wise therapy. The use of the iodoform pack against the exposed bleeding uterine sinuses was also intelligent. The treatment of the case after it fell into intelligent hands was ideal.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

DEATH

CHAMBERLAIN — THEODORE CHAMBERLAIN, M.D., of Concord, died August 8. He was in his seventy-second year.

Dr. Chamberlain received his degree from Columbia University College of Physicians and Surgeons in 1895. He was former district medical examiner and consulting physician to Middlesex School and the Concord Reformatory.

He was a former member of the Massachusetts Medical Society and a member of the Harvard Club of Boston.

His widow, eight children, four grandchildren and a brother survive him.

CONVALESCENCE*

Of your many friends and acquaintances who may have made you listen by the hour to the details of their operations or grave illnesses, I can safely wager that not one has said much about how long it was before he felt like himself again. An operation or serious illness is a drama — in which fear and worry play an important part. By comparison, the slow period of getting well — which we call the convalescent period — seems of little importance. Convalescence is an anticlimax which gets little notice and almost no respect.

Actually, convalescence is — contrary to popular impression — every whit as important as the healing of the surgical wound or the safe passing of the pneumonia crisis. For after damaged tissues have healed or infection has been banished, the body itself must be given time in

*A "Green Lights to Health" broadcast given by Dr. F. Dennette Adams on Wednesday, May 31, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

which to recover. Its exquisitely sensitive nervous system responds to every hurt to the body — like a weather vane to every breath of wind — and, what is more important, recovers slowly. That is why, even when your appendix is out and the wound healed, or the fever of an infection is gone, you are still not well: you may be weak, listless, without appetite, irritable and perhaps depressed. Your nervous system has been disorganized and has not yet returned to normal. Muscular tone, too, because of inactivity and lack of exercise, is at its poorest. Resistance is at its lowest; debility at its highest.

Convalescence is the period in which the whole body — as apart from the special organ or part affected by disease — recovers from the shock of the operation or illness. It is the interval in which lost nervous energy comes back and muscular tone is restored. A sufficient period of recuperation is the deciding factor which makes the difference — all other things considered — between a complete or partial recovery from illness. Since the body's supply of "pick-up" power has been drained, the best insurance against the development of some complication or of an entirely different ailment is to take enough time off to get really well.

It has been found that many anxieties and worries, and other forms of nervous disturbance, follow operations and illnesses if the patient is permitted to resume his ordinary life without a sufficiently long period of recuperation. Every medical consultant sees such cases from time to time.

A typical instance of incomplete recovery is the case of a twenty-five-year-old school teacher, who consulted her physician because of weakness and frequent crying spells. She was haunted by the idea that these were due to some dread disease. In fact, she was on the point of giving up her position. A thorough examination revealed no organic trouble: the heart, lungs and kidneys were normal, as were the blood tests; there was no evidence of hidden infection. Careful questioning revealed no family, economic or social problems that might account for her emotional upsets. But, a month before, her tonsils had been removed; she had been discharged from the hospital in three days, and ten days later had returned to work. To anyone familiar with the emotional and physical drain which follows any operation or illness, it was quite evident that she was suffering the consequences of too short a convalescence. When the young lady was told this, she protested. Various of her friends, she said, had returned to work shortly after having had their tonsils removed without experiencing any trouble like hers. She was sure there must be something else wrong. However, she was persuaded to take a three weeks' vacation. When she returned from this rest, a refreshed, healthy young woman, her weakness and depression entirely gone, she was willing to admit that perhaps going to work too soon had been the cause of her trouble.

I could tell you of many similar instances. In serious illnesses such as pneumonia, for example, and in long surgical operations, the drain on the human system is very much greater. The pain, fever, loss of sleep and inability to eat that accompany grave illness, the damage to the tissues of the body and loss of blood from an operation, the nausea and vomiting which often follow ether and other anesthetics, all these heavily tax the body. Added to these physical factors are the emotional disturbances: worry over the outcome of one's illness or operation; fear and worry about the doctor's, the nurse's and hospital's bills; anxiety over the welfare of one's family, one's job or the condition of one's business.

Think for a moment of how fagged out and nervous you are after a night made sleepless by worry, a barking dog or a poor mattress. Or how weak and irritable a week's bout with grippe leaves you. Multiply these sensations a thousandfold and you will realize how miserable one is after the ordeal of a serious illness.

Yet most of us, whether just out of the hospital or merely getting over a severe cold, expect to get out of bed and go back immediately to normal duties — perhaps driving a truck, pounding a typewriter or caring for a family of six. We believe that now the bothersome appendix is out or the fever gone, we ought to have back our health and be as strong as ever. But as has already been explained, that is far from true. This kind of thinking is dangerous and may lead to serious trouble.

We must realize that getting over any illness requires time. Time and expense are the most difficult hurdles in the way of the convalescent. No rigid rule governing the length of recuperation can be laid down; depending on the nature of the case, it may take three weeks or three months for complete recovery. As a rule, the ideal place for convalescence is a hospital, sanatorium or health resort, where proper diet, sufficient rest, quiet surroundings and perhaps supervised exercise are possible. But, to be satisfactory, such a place must be one in which peace of mind and rest for the spirit are also possible. Homesickness, worry over expense or unhappiness in the strange surroundings can nullify whatever beneficial effects such institutions may have. In such cases, the patient may be much better off convalescing at home, but only if he can be kept away from family cares and disturbances.

One can compromise with almost any situation. If it is not possible to put off returning to work, then the burden must be lessened by working only half-days at first, taking rest periods during the day and sleeping twelve or fourteen hours instead of the usual seven or eight.

Above all, the convalescent must put himself in the right frame of mind. Do not expect to rise from a hospital bed restored to perfect health two weeks after an illness. Be prepared to feel weak, nervous, irritable; know these feelings for what they are: Nature's warning that the repairs are not yet finished and the engine not yet ready for you to step on the gas.

* * *

Q. Why is it that so simple a thing as a severe cold often leaves one depressed and weak?

A. Even a cold starts the same physical and emotional processes which, in a much greater degree, cause the nervous irritability and muscular debility which follow more serious illness.

Q. Why does a person recovering from pneumonia, which is essentially a disease of the lungs, have other complaints such as poor appetite, digestive difficulties or profuse sweating?

A. Disease, whatever its nature, attacks not only the particular organ or part — as in the case of pneumonia, the lungs. To some extent all the other organs of the body are affected. The battle with the disease has drained the body of all its resources; hence, all the other organs and parts are, for the time being, exhausted.

Q. Why does one often feel depressed or irritable after sickness?

A. As I have said, the nervous system has also been burdened during the illness by such factors as pain, loss of sleep, perhaps insufficient nourishment and, especially, worry either over oneself, one's family or one's business.

It is this nervous exhaustion that causes the irritability, depression, tendency to cry or other signs of emotional disturbance. The patient is left with no stamina, either emotional or physical.

Q. My impression, and I think it is a fairly general one, has always been that ten days to two weeks is enough for recovery from a severe illness or a surgical operation. You said that such a period is not long enough. Why?

A. The amount of time you mention is sufficient only for the healing of the tissues which have been directly affected by the disease or operation. This is not time enough for the patient himself to regain either his normal mental energy or his physical strength. His storage batteries have been exhausted. In order to work as well as they formerly did, they need to be completely charged by the magnetos of food, sleep and exercise. If they are not fully charged, you cannot depend on them to do the things they were meant to do. The bells will not always ring when you press the button. It saves time to spend time in getting really well after you have been really sick.

MISCELLANY

NEW BUILDING AT THE SALEM HOSPITAL

The trustees of the Salem Hospital are proceeding with the necessary detailed plans for the erection of a maternity and children's building. The building committee of the trustees, Walter E. Poor, chairman, has given final approval this week to the general building plans, including three complete stories and a fourth story of half the area. This building will extend southeasterly from the axis of the main building one hundred and ninety-three feet. It will be forty-three feet wide in the main portion and fifty-one feet wide in other sections.

The ground floor will contain a children's ward, including a play room, four private rooms, sixteen beds in cubicle units, a babies' cubicle ward of six beds, a six-bed recovery room, and an observation department with separate services and facilities. The usual technical and service facilities typical to hospitals will be available, such as utility rooms, bathrooms, nurses' station, diet kitchen, and so forth.

The second floor will be for ward and semi-private maternity patients, including accommodations for eight patients in two-bed rooms, twenty patients in four-bed cubicle-curtained wards, the usual service facilities, a nursery with cubicles for each baby, an isolation department with accommodations for four patients in single rooms, and a waiting room.

On the third floor will be accommodations for private maternity patients, including seventeen private rooms, sitting room, waiting room, all the necessary services, two nurseries for premature babies and an isolation nursery. All nurseries will be air-conditioned so that proper humidity will be available for the babies.

The fourth floor will be devoted to the delivery suite, including two two-bed labor rooms, three delivery rooms, nurses' dressing room, doctors' room and nursery for the newborn babies.

This plan as outlined will have accommodations for forty-nine maternity patients and thirty-two children, and will, in addition, release the present facilities occupied by the maternity and children's departments for medical and surgical patients, thus relieving the crowded conditions in these departments, as well as providing the most modern facilities for maternity patients and children.

This completes the building program begun last year with the erection of an intermediate building. This contains in the basement a large assembly room for lectures and conferences, accommodating two hundred people, accessible through a separate entrance; on the next floor a modern x-ray department with a deep-therapy room, a radiographic room, dark rooms, a fluoroscopic room, a cystoscopic room and office; and on the floor above, which is the main floor of the hospital, a staff room with a large and comfortable library adjacent to it, a room for the interns and several consultation rooms. The corridor of this floor will be the main corridor connecting the entrance floor of the main hospital building with the new maternity building.

CORRESPONDENCE

PREMARITAL BLOOD EXAMINATIONS IN NEW YORK STATE

To the Editor: The New York State Legislature in 1938 passed a law requiring a physical examination including a standard serological test for syphilis on all applicants for marriage licenses within the State.

Several instances have been called to my attention in which residents of other states have had difficulties in securing marriage licenses in New York State because of misinterpretations of the law by themselves or their examining physicians. In order that such inconveniences may be avoided, I should greatly appreciate it if you would, through your journal, inform the medical profession of your state of the provisions of the New York law.

That part of the act as amended and effective July 1, 1939, referable to these examinations reads as follows:

> *Physician's examination and serological test of applicant for marriage license.*
>
> (1) Except as herein otherwise provided, no application for a marriage license shall be accepted by the town or city clerk unless accompanied by or unless there shall have been filed with him a statement or statements signed by a duly licensed physician or by a commissioned medical officer of the United States army, navy or public health service that each applicant has been given such examination, including a standard serological test, as may be necessary for the discovery of syphilis, made on a day specified in the statement, which shall not be more than the thirtieth day prior to that on which the license is applied for, and that in the opinion of the physician the person therein named is not infected with syphilis, or if so infected is not in a stage of that disease whereby it may become communicable. . . .

The law further states that "a standard serological test shall be a laboratory test for syphilis approved by the state commissioner of health and shall be performed by the state department of health, or in the City of New York by the department of health of such city, or at a laboratory approved for this purpose by the state department of health, or in the City of New York, by the department of health of such city."

I offer the following comments relative to its interpretation:

1. A duly licensed physician means any physician duly licensed to practice medicine in the state in which he resides or in which he maintains his office.

2. The date of examination is interpreted to mean the date on which the specimen of blood is taken.

3. The state commissioner of health and the state department of health referred to mean the commissioner of health of the State of New York and the New York State Department of Health.

4. Laboratory tests made as a part of premarital examinations for persons applying for marriage licenses in New York State, outside of New York City, as well as the laboratories in which these tests are performed, must be approved by the New York State commissioner of health. For administrative reasons laboratories within New York State only have been approved for tests on applicants for licenses in the State exclusive of New York City.

5. The Commissioner of Health of the City of New York has approved certain out-of-state laboratories for the performance of serological tests on persons applying for marriage licenses in New York City. Requests for information concerning laboratories approved by the New York City Department of Health should be addressed to that department at Worth and Centre Streets, New York City.

Outline of procedures for examination of out-of-state applicants for marriage licenses in New York State exclusive of New York City.

1. Any physician duly licensed to practice medicine in the state in which he resides or in which he maintains his office may perform the necessary physical examination.

2. The specimen of blood must be sent to an approved laboratory in New York State. It is suggested that specimens be sent to the Division of Laboratories and Research, New York State Department of Health, New Scotland Avenue, Albany, New York, where examinations will be made free of charge.

3. The specimen should be labeled "for premarital examination."

4. The use of air mail is recommended when the specimen must be sent a great distance.

5. Upon completion of the test the laboratory will send the physician, in addition to the usual laboratory report, a certificate to the effect that the serological test was performed as a part of a premarital examination.

6. If, in the opinion of the examining physician, the applicant is free from syphilis or does not have the disease in a stage which may become communicable, he should complete the certificate as indicated thereon.

7. The certificate is given to the applicant who will submit it to the clerk when the marriage license is applied for.

If these procedures are followed, there should be no difficulty in obtaining the license.

For further information relative to the marriage of persons in New York State, exclusive of New York City, communications should be addressed to the Division of Syphilis Control, New York State Department of Health, Albany, New York.

EDWARD S. GODFREY, JR.,
Commissioner of Health.

Albany, New York.

A NOTE OF THANKS

To the Editor: Retiring from the position of physician-in-chief, as I do on September 1 next, I take this opportunity to express my thanks to the many physicians who, since the Peter Bent Brigham Hospital opened its doors for medical patients, have co-operated by answering follow-up letters about their patients sent to the medical wards of this institution. Information, thus so generously given to us, has been of great value in completing our records, oftentimes clearing up difficulties in diagnosis and increasing our knowledge of prognosis. I appreciate greatly the trouble these men have taken to give to us information about such patients subsequent to discharge from the hospital and utilize this method of expressing my gratitude.

HENRY A. CHRISTIAN.

721 Huntington Avenue,
Boston.

REPORTS OF MEETINGS

HARVARD MEDICAL SOCIETY

A regular meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on April 25, with Dr. Elliott C. Cutler presiding. The speaker of the evening was Dr. Francis G. Blake, Sterling Professor of Medicine at Yale University School of Medicine, whose subject was "The Clinical Use of Sulfapyridine in Coccal Infection."

Instead of the usual presentation of cases, Dr. Blake appropriately recounted his first experiences with the serum treatment of pneumococcal infections while resident physician at the Peter Bent Brigham Hospital in 1915. At that time, two interns contracted typical lobar pneumonia while on duty. After three anxious days, the typing was completed, and the first specific pneumococcal antiserum was administered at the hospital. Due to the delay in instituting therapy, however, the results were sadly disappointing, with one young doctor dying and the other recovering only after a prolonged course complicated by empyema. Despite such a dismal failure, which was not an uncommon occurrence at that time, everyone is now acquainted with the vast improvements in the technics of typing sputum and blood, as well as in the process of manufacturing and administering antiserums. Dr. Blake then turned to an evaluation of sulfapyridine in a comparable stage in its development. He said that he believes that the problem should not be complicated by the use of serum plus sulfapyridine during this probationary period. He is further inclined toward the opinion that the drug is unnecessary when serum therapy is being employed in a given case. His main conclusions, therefore, were based on statistics gathered from 51 typed cases of pneumococcal pneumonia treated solely with sulfapyridine and a scattering of small groups of other coccal infections. The mortality among the pneumococcal pneumonias was 5.8 per cent, one of the three deaths occurring in a patient in whom therapy was not instituted until the eighth day. The majority of these cases exhibited marked decrease of fever within twenty-four hours, and in the remainder the fever subsided within forty-eight hours. These statistics, though not numerically significant, are appreciably better than those in the serum-treated cases due to types which are likely to respond favorably, and inestimably better than those in cases of all types for which serum is available. For instance, the best results reported in Massachusetts are in Type 1 pneumonia with a mortality of 8.7 per cent, whereas Type 2 pneumonia,

which is considered favorable for serum treatment, still carries with it a mortality of 27 per cent. Despite the fact that mortality figures have been reduced by serum treatment as much as 75 per cent in cases due to certain types, the number of survivors with sulfapyridine is much greater.

Dr. Blake's results in other coccal infections have not been striking, although only a few cases have been treated. Thus, he considers sulfapyridine no more efficacious than is sulfanilamide in combating hemolytic streptococcal infections, and advises against its substitution in this instance. Furthermore, the drug has shown nothing to recommend its use in staphylococcal infections, nor have the results in mixed infections been remarkable.

Since it has been considered that the efficiency of sulfapyridine in combating infection might conceivably be proportional to its level in the blood stream, the New Haven group has studied this problem. The dosage employed is 2.0 gm. immediately and then 1.0 gm. every four hours by mouth. On this regimen, 70 per cent of the patients have a level in the circulating blood of 5 to 10 mg. per 100 cc. in thirty-six hours, while 20 per cent show less than 5 mg. and 10 per cent are between 10 and 15 mg. Probably the most important factor regulating this level is the degree of acetylation of the sulfapyridine in the body. This therapeutically inactive derivative varies greatly despite the mode of administration of the sulfapyridine, and the percentage of this form in any given patient is entirely unpredictable. Not only does the amount of acetylation fluctuate, but also the rate at which this conjugation occurs, so that some patients show a gradual increase from 15 to 30 per cent in this form, while others show an immediate conversion of 50 per cent to the inactive form, which eventually rises to 80 per cent. The relation of the presence of large amounts of acetylated sulfapyridine with untoward reactions has been suggested, but as yet there is no conclusive proof that any such correlation exists. For example, there have been patients with a high percentage of the acetylated product who have shown no unusual manifestations; however, those who have appeared toxic invariably showed a rapid and high conversion.

The necessary or desirable level of sulfapyridine which should obtain for prompt therapeutic response is another moot point. In Dr. Blake's series, a level as low as 3.5 mg. per 100 cc. was sufficient to bring about a satisfactory response in a patient who was a known diabetic and in whom treatment was not begun until the second day. There have been 10 additional cases in which a critical recovery occurred with a blood sulfapyridine of less than 5 mg. per 100 cc., while 2 failed to exhibit a satisfactory response despite a level above 5 mg. It is known, therefore, that although some cures occur when less than 5 mg. per 100 cc. of sulfapyridine are circulating in the blood stream, such a concentration does not insure recovery.

It was often noted among the earlier patients that relapses were not uncommon when chemotherapy was discontinued after a period of two or three days. It was suggested by Dr. Blake, therefore, that the administration of the drug should be continued until about the seventh day, when some natural immunity may be expected.

The most obvious and frequent disadvantage of sulfapyridine is nausea and vomiting, which occurred to some degree in 60 per cent of those treated. In only one third of this number, however, was the result serious enough to warrant substitution of parenteral for oral administration of the drug. This unpleasant complication may occur as early as the fourth hour and lasts about four days. The mechanism involved is probably a central reaction rather than a local one on the gastric mucosa, for parenteral injection does not obviate the difficulty. This should not be accepted too categorically, however, for even parenterally administered fluids rapidly find their way into the gastrointestinal tract.

Since regurgitation of the drug depresses its level in the blood, some other mode of administration must be employed in such cases. The usual method at New Haven has been the use of hypodermoclysis twice a day. Since sulfapyridine is not soluble in distilled water, various vehicles were tested until it was determined that a 0.2 per cent solution of the drug in one containing 5 per cent glucose and 0.85 per cent sodium chloride would remain stable for four days at 16°C. This solution has given no untoward reactions, either by clysis or by the intravenous route. A combination of these two parenteral routes produces a rapid rise in the blood level and a good maintenance of it in critical cases. The variation in assimilation of sulfapyridine is not affected by parenteral injection, however.

Other reactions observed by Dr. Blake are entirely comparable to those which occur following the use of sulfanilamide, but with the important addition of acute renal symptoms. Nine of his 130 patients experienced acute hematuria, 4 of these with gross blood and violent colic. Some showed only microscopic blood; and all recovered satisfactorily, either after discontinuing treatment in the more severe instances or despite treatment in the mild cases. Another important toxic manifestation enumerated by the speaker included drug fever, which occurs on the fifth to the eleventh day and may simulate serum sickness if serum therapy has been used. Fourteen such cases have been diagnosed, but no relation to the amount or duration of treatment could be determined. One case each of hemolytic and severe hypochromic anemia were reported, both the patients recovering promptly when sulfapyridine was omitted. Three patients showed moderate degrees of leukopenia which were prevented from progressing to agranulocytosis by prompt interruption of therapy. He emphasized the tremendous importance of accurate daily hematological studies on patients receiving sulfapyridine.

In commenting on the use of the drug in pneumococcal meningitis, Dr. Blake pointed out the correlation between the level of sulfapyridine in the spinal fluid and blood with the culture of the cerebrospinal fluid. Although only 1 case had been treated, and that with the addition of serum, it is significant that the culture remained negative when the level was greater than 5 mg. per 100 cc. but was positive whenever the level dropped below that point due to discontinuance of intrathecal sulfapyridine.

In conclusion, Dr. Blake reiterated that sulfapyridine appears "extremely promising" in pneumococcal infections, but that due caution should be exercised lest it be used indiscriminately by those not aware of its potential dangers.

Dr. O. H. Perry Pepper, of Philadelphia, reported the results of a group of investigators who had organized a similar experiment in the twelve leading hospitals in that city. These statistics concerned 500 cases treated with sulfapyridine exclusively. In so far as possible, these cases were examined, x-rayed, typed and cultured under the jurisdiction of an official committee, so that adequate data are available. Four hundred of these cases were typed; the mortality in this group without positive blood culture was 7 per cent, while those with bacteremia showed a death rate of 22 per cent. In the 100 untyped or nontypable cases, the mortality amounted to 10 per cent. These data agree very closely with those of Dr. Blake.

Dr. Pepper also said that the manufacturers had stated that there have been reports of recurrences occurring with the same type of pneumococcus after many weeks or months. These are not relapses, since they usually occur long after convalescence has been complete. Dr. Pepper added a new reaction, namely severe mental reactions in about 3 per cent of the patients; no fatalities were recorded as being due to the drug.

Dr. Lewellys F. Barker, after recounting a successful personal experience with sulfapyridine, reported on the progress being made in Baltimore with the drug. Drs. Marshall and Long have perfected a sodium salt of sulfapyridine so that an adequate dosage may be administered parenterally without the disadvantages of the large volume of fluid necessary with the relatively insoluble pure product. This new compound, however, is strongly alkaline and can consequently be given only by the intravenous route. That there is an inherent danger in this substance has been proved by the fall of blood pressure, decreased respiratory rate and depressed renal function in dogs given five times the usual maximum dose. The amount necessary to attain an adequate level in human beings is only 0.05 gm. per kilogram as contrasted with the toxic dose of 0.5 gm. in the dogs. Given in such doses in a 5 per cent solution, there is a rapid and equal distribution in the blood and tissues at a level of 5 to 8 mg. per 100 cc. in a very few minutes. Due to the potential toxicity of this sodium salt, it has not been used by the Baltimore workers except when specific indications exist. It should always be administered slowly (5 cc. per minute) and any leak into the tissues should be carefully avoided. It has been used in very severe cases: in two injections, six to eight hours apart, together with the usual dosage by mouth. It also finds a place in cases in which there is poor absorption orally so that the temperature fails to drop below 101°F. rectally and the blood level of the drug remains below 4 mg. per 100 cc. The final indication for its use is in cases in which there are severe nausea and vomiting.

Dr. Alvah H. Gordon said that in using sulfapyridine at the Montreal General Hospital an attempt had been made to give the patients the best possible treatment. It was therefore determined not to continue its use if there was no fall of temperature within twelve hours in any proved case of pneumococcal pneumonia. It is a significant commentary that only 3 of 68 patients required serum treatment under this regimen. The mortality rate in all cases treated with sulfapyridine was 8.8 per cent, which is half that for all typable pneumonias under serum treatment. Dr. Gordon stated that they had also experienced difficulty in producing and maintaining proper blood levels, but he also observed that lack of a supposedly satisfactory level does not preclude the possibility of recovery, nor does an unusually high level always assure a favorable prognosis.

Dr. Warfield T. Longcope reported on work carried on at Johns Hopkins Hospital with Dr. W. Barry Wood. Of 83 cases of pneumonias treated with sulfapyridine since February, the mortality was 4.8 per cent. The virulence of the infection, however, was not high during this period for only 12 per cent exhibited bacteremia, in contradistinction to 30 per cent earlier in the year. The average duration of convalescence was 3.3 days with chemotherapy and 6.7 days with serum treatment. Dr. Longcope noticed that patients treated with sulfapyridine do not look detoxified even when their temperature drops at first. Furthermore, careful x-ray examinations show evidence of a further extension of the pathologic process when the temperature has already returned to normal. Both these facts lend support to the theory that the infection is only in abeyance during early convalescence and that relapses are prone to occur during this period if treatment is interrupted.

Dr. Longcope also reported some illuminating experiences with the urinary complications of sulfapyridine therapy. It has been shown in animals that the acetylated compound is precipitated in large amounts in the kidney pelves. One of their unsuccessful cases, in which the patient failed despite an adequate initial response and the maintenance of a high blood level, exhibited great numbers of these crystals in the ureters and kidney pelves. Indeed, the finding of such crystals in concentrated urines of dehydrated patients is not uncommon in sulfapyridine treatment. Dr. Longcope believes that despite the enormous encouragement offered by various reports, sulfapyridine will not be relied on exclusively. It does seem to him, however, that the combination of this chemotherapy with refined antipneumococcus serum may materially alter the outlook for pneumonia.

Dr. Duncan Graham, of Toronto, admitted that he has never been quite satisfied with the serum treatment of pneumonia, and does not consider the addition of sulfapyridine gratuitous. He originally intended to maintain a serum-treated group as a control but soon abandoned the plan when it became obvious that the mortality was so high in the control group that these patients should not be denied the benefits of sulfapyridine. Of 100 cases with and without bacteremia, Dr. Graham obtained a mortality of 10 per cent, with no deaths under forty years of age. His dosage for the first twenty-four hours was somewhat larger than that advocated by others, his patients receiving 2.0 gm. every four hours for six doses. This usually gave a blood sulfapyridine level of 7 to 8 mg. per 100 cc., and it was believed that cases with levels above 10 mg. should be suspected as being due to renal damage. He added that, if no decrease in temperature occurs in twenty-four to thirty-six hours, one should suspect that either a mixed infection or some complication is present. On the other hand, a rising temperature during the course of treatment usually indicates drug fever. An occasional patient with leukopenia may develop a fever due to decreased resistance, but this fever should fall again when the leukocyte count recovers. Thus, careful leukocyte counts are of inestimable value in determining the etiology of certain bizarre reactions. Dr. Graham added that he also had encountered troublesome hematuria among those treated with sulfapyridine. No liver damage was in evidence, however, and the bile in the urine disappeared under treatment.

Dr. Alfred W. Harris concluded the summary with a short résumé of the cautious use of sulfapyridine at the Peter Bent Brigham Hospital. He said that the drug had been used, in alternation with sulfanilamide, only in cases for which serum was unavailable. There was only 1 death in 18 patients, while in the sulfanilamide-treated group 4 of the 32 cases ended fatally.

The consensus among this group of men, each of whom varied in the intensity of his enthusiasm, seemed to be that an indispensable weapon has been added to the armamentarium for fighting pneumococcal pneumonias, but that it remains problematical whether sulfapyridine will entirely supplant or merely complement the still progressing serum therapy.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Monday, August 21

Tuesday, August 22

*10 a. m.–12:30 p. m. Boston Dispensary tumor clinic.

Friday, August 25

*10 a. m.–12:30 p. m. Boston Dispensary tumor clinic.

Saturday, August 26

*10 a. m.–12 m. Staff rounds of the Peter Bent Brigham Hospital. Conducted by Dr. Robert T. Monroe.

*Open to the medical profession.

August 30–September 2 — Seminar in Physical Therapy. Page 857, issue of May 18.

September — Boston Psychoanalytic Institute. Page 450, issue of September 22, 1938.

September 4–6 — Institute for the Consideration of the Blood and Blood-Forming Organs. Page 941, issue of June 1.

September 4–6 — Institute at University of Wisconsin Medical School. Page 160, issue of July 27.

September 5–8 — American Congress of Physical Therapy. Hotel Pennsylvania, New York City. Page 857, issue of May 18.

September 11–15 — American Congress on Obstetrics and Gynecology. Page 938, issue of December 8.

September 14–16 — Biological Photographic Association. Page 941, issue of June 1.

September 15–28 — Pan-Pacific Surgical Association. Page 863, issue of November 24.

October 23–November 3 — New York Academy of Medicine. Page 977, issue of June 8.

Fall, 1939 — Temperature Symposium. Page 218, issue of February 2.

December 2 — American Board of Obstetrics and Gynecology. Page 1019, issue of June 15.

January 6, June 8–11, 1940 — American Board of Obstetrics and Gynecology. Page 160, issue of July 27.

March 7–9, 1940 — The New England Hospital Association. Hotel Statler, Boston.

May 14, 1940 — Pharmacopoeial Convention. Page 894, issue of May 25.

June 7–9, 1940 — American Board of Obstetrics and Gynecology. Page 1019, issue of June 15.

BOOK REVIEWS

Problems of Ageing: Biological and medical aspects. Edited by E. V. Cowdry. 758 pp. Baltimore: Williams & Wilkins Co., 1939. $10.00.

Professor Cowdry, widely known as a scholar and teacher, is to be warmly congratulated for his successful editing of this valuable book, to which twenty-five eminent scientists have each contributed a chapter and which is sponsored by the Josiah Macy, Jr., Foundation. Professor Cowdry writes in the preface: "The opportunity to bring to bear on the problem the experience and points of view of many specialists, working together in a constructive way, has been unrivaled." Mr. Lawrence K. Frank writes in the foreword: "The problem of ageing therefore is not a purely biological question, but has large cultural, social and psychological implications. Single cause and effect relationships can scarcely be considered in such total organic interactions; they must be supplemented, or perhaps replaced, by a broader conceptual picture of the functioning organism as a 'field' (to borrow the term from physics) in which the totality and the parts are dynamically interrelated and therefore are continuously reacting to each other and to the environment." Professor John Dewey, of Columbia University, writes in the introduction: "Biological processes are at the roots of the problems and of the methods of solving them, but the biological processes take place in economic, political and cultural contexts. We need to know the ways in which social contexts react back into biological processes as well as to know the ways in which the biological processes condition social life. This is the problem to which attention is invited."

The quotations offered the reader give merely a glimpse of the importance of the material presented by the contributing authorities. It is impossible at this time to give a detailed review of each chapter; however, much stimulation will come to the reader by noting the title and author of each chapter: "Ageing in Plants," William Crocker; "Senescence and Death in Protozoa and Invertebrates," H. S. Jennings; "Ageing of Insects," L. O. Howard; "Ageing of Vertebrates," T. Wingate Todd; "Human Cultural Levels," Clark Wissler; "Longevity in Retrospect and in Prospect," Louis I. Dublin; "Cardiovascular System and Blood," A. E. Cohn; "Lymphatic Tissue," E. B. Krumbhaar; "Digestive System," A. C. Ivy; "Urinary System," Jean R. Oliver; "Skeleton, Locomotor System and Teeth," T. Wingate Todd; "Ageing of the Skin," F. D. Weidman; "The Thyroid, Pancreatic Islets, Parathyroids, Adrenals, Thymus and Pituitary," A. J. Carlson; "Female Reproductive System," Edgar Allen; "Male Reproductive System," Earl T. Engle; "Changes in Personality and Psychosexual Phenomena with Age," G. V. Hamilton; "Ageing of the Nervous System," Macdonald Critchley; "The Eye," Jonas S. Friedenwald; "The Ear," Stacy R. Guild; "Psychological Aspects of Ageing," Walter R. Miles; "Chemical Aspects of Ageing," C. M. McCay; "Ageing of Homeostatic Mechanisms," Walter B. Cannon; "Ageing of Tissue Fluids," E. V. Cowdry; "Ageing Processes Considered in Relation to Tissue Susceptibility and Resistance," W. deB. MacNider; "Ageing From the Point of View of the Clinician," Lewellys F. Barker.

A most useful feature of this book is the inclusion of a summary and a list of references at the end of each chapter. The illustrations are well chosen and there is an excellent index. This book becomes indispensable to everyone who would understand the problems of ageing. It is further recommended to all students of biological thought as a book which merits study and constant reference.

The Newer Knowledge of Nutrition. E. V. McCollum; Elsa Orent-Keiles and Harry G. Day. Fifth edition, entirely rewritten. 701 pp. New York: The Macmillan Co., 1939. $4.50.

This book, in its fifth edition, is devoted to the problems of nutrition of the body and has been written by three members of the faculty of Johns Hopkins University. The fourth volume was published in 1929 but was soon exhausted and has been out of print for several years. Since then the knowledge relating to the nutrition of human beings has been enriched by the discovery of many facts by research workers in many fields, and the authors have revised and rewritten the material hitherto published, with the addition of more recent contributions to the subject.

The book opens with a résumé of the historical background of the works of earlier years which led to the present understanding of how health is maintained and prepares the reader for the unfolding of the mysteries which seemed beyond solution for many generations, when the knowledge of those earlier periods was not founded on scientific study but generally on experiments of trial and error. In the second chapter the methods employed by Magendie, Voit and many other workers for learning about the essential nutritive requirements of the body are described, with the associated implications when the individual is deprived of these important elements; and in the next nine chapters the carbohydrates, lipids, proteins, amino acids and mineral elements are given their appropriate places in the nutritional scheme.

Then follow twelve chapters devoted to the vitamins,

in which there is convincing evidence of the great advances which have followed careful study of each of the long list of these elements now recognized. Even so it is plainly stated that, although the source and behavior of vitamins have been made clear, in many instances there yet remains a great deal to be accomplished in clearing away the uncertainties about some of them, although chemical studies have succeeded in establishing the formulas of many. These chapters will instruct the biochemist more than the average physician, although the therapeutic value of each vitamin is set forth.

Later chapters describe the dietary properties of foodstuffs, with explanations of the causes of normal and perverted appetites, and the foods of people living in various regions of the earth. The chapter on the essential nutrition of the teeth and the evil effects of caries is of especial interest to civilized people.

This book is a valuable addition to the literature pertaining to human well-being, and aside from those parts of especial interest to research workers, the practical aspects of the newer facts set forth can be utilized by the average reader because there is a careful avoidance of too many technical terms.

Where illustrations, graphs and tables help to make clear the subject under discussion they are freely used and are well constructed. Every medical student, doctor and dentist should have this volume available for study.

Chronic Intestinal Toxemia and Its Treatment: With special reference to colonic therapy. James W. Wiltsie. 268 pp. Baltimore: William Wood & Co., 1938. $3.00.

This book is an attempt to indict the colon as a focus of infection and as a source of chronic intestinal toxemia and to prove that colonic therapy, particularly colonic irrigation, is a rational and effective method of treatment for chronic infection. This is a difficult task in these days when colonic irrigation has been so generally discredited, and in spite of sixteen disjointed chapters, it is not accomplished. The book is verbose and illogical, and although citations are used from 180 papers concerning the colon, in most instances their authors would unquestionably fail to subscribe to their application to this context. The book was obviously intended to place the procedure of colonic irrigation on a scientific basis — an accomplishment which cannot, however, be granted by the reviewer.

Laboratory Manual of the Massachusetts General Hospital. Francis T. Hunter. Third edition, thoroughly revised. 119 pp. Philadelphia: Lea & Febiger, 1939. $1.75.

In 1922, a group of medical interns at the Massachusetts General Hospital did a useful bit of work. Drs. R. R. Wheeler, Joseph Stokes, J. E. Wood and Isaac Starr prepared a pocket outline of the routine laboratory work done by interns in this hospital. They received sage editorial advice from Drs. R. I. Lee, W. H. Smith and A. V. Bock. The upshot of the matter was an attractive booklet which became guide and friend to many interns and practitioners.

In 1928, Drs. Wheeler and F. T. Hunter prepared a second edition of this outline. It was short, attractively dressed in flexible cover so as easily to fit into one's pocket, not too expensive, and thoroughly readable. It was favorably reviewed by such authorities on medical literature as the *Journal of the American Medical Association* (*92*:256, 1929) and the *Archives of Internal Medicine* (*43*:570, 1929). Each said about the same thing: that the book was not intended to cover its subject matter exhaustively but to describe in few words how to carry out different essential procedures with speed and accuracy and that it accomplished this aim with notable skill.

The third edition brings the manual up to date. It contains nineteen pages more than the second edition but no wonder, considering the various laboratory innovations which have been introduced in recent years. It continues to strive for simplicity and directness. It is bound to prove popular for it contains so much in the way of practical information admirably presented.

Science in Progress. Edited by George A. Baitsell. 322 pp. New Haven: Yale University Press, 1939. $4.00.

These are semi-popular lectures given under the auspices of the Sigma Xi Society. They serve as an excellent means for not only popularizing science but also bringing to the attention of physicians important advances in allied fields of medicine. The most useful papers from this point of view are those by W. M. Stanley, of the Rockefeller Institute for Medical Research, on "Recent Advances in the Study of Viruses," L. O. Kunkel, also from the Rockefeller Institute, on "New Views in Virus Disease Research," Karl E. Mason, from Vanderbilt University School of Medicine, on "Vitamins and Hormones," R. R. Williams on "The General Role of Thiamin in Living Things" and Francis G. Benedict on "Animal Metabolism: From mouse to elephant." Other papers consider "Internal Secretions in Reproduction," "Recent Developments in Our Knowledge of Chromosome Structure and Their Application to Genetics" and "Electrical Potentials of the Human Brain."

Williams's work on thiamin is well known as he was the first to synthesize this vitamin. Benedict's paper on animal metabolism is not only interesting and constructive but also amusing, as he tells in a delightful manner his twenty-five-year search for an elephant that could be used for metabolic studies. He finally found one while walking along a street in New York, and this elephant proved to be valuable in his research, although his work was not without considerable difficulty. As an example of persistency in research, Benedict's elephant work has rarely been surpassed.

All these papers are of a high standard and constitute, as Professor Harlow Shapley says in the preface, "a significant contribution to the panoramic view of science from which men must build their vision of the future."

The Circulation of the Brain and Spinal Cord: A symposium on blood supply. The proceedings of the Association for Research in Nervous and Mental Disease, New York, December 27 and 28, 1937. 790 pp. Baltimore: Williams & Wilkins Co., 1938. $10.00.

This is a large book containing the papers given at a meeting of the Association for Research in Nervous and Mental Disease in December, 1937, under the chairmanship of Dr. Wilder Penfield, of Montreal. The volume summarizes our present-day knowledge of cerebral circulation. In addition to the reports of research, a critical discussion of the symposium is given by Dr. Stanley Cobb. This last chapter is concise, timely and in every way admirable. To the reviewer, this volume is the best of the long series published by the association and augurs well for the continuation of the yearly reports of this unique organization, dedicated to co-ordinated research.